CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761025Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION[1]

NDA # BLA # 761025	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type: *(an action package is not required for SE8 or SE9 supplements)*
Proprietary Name: Praxbind® Established/Proper Name: idarucizumab Dosage Form: Solution		Applicant: Boehringer Ingelheim Pharmaceuticals, Inc. Agent for Applicant (if applicable):
RPM: Alycia Anderson		Division: Division of Hematology Products

NDA Application Type: ☐ 505(b)(1) ☐ 505(b)(2)
Efficacy Supplement: ☐ 505(b)(1) ☐ 505(b)(2)

BLA Application Type: ☐ 351(k) ☒ 351(a)
Efficacy Supplement: ☐ 351(k) ☐ 351(a)

For ALL 505(b)(2) applications, two months prior to EVERY action:

- **Review the information in the 505(b)(2) Assessment and submit the draft[2] to CDER OND IO for clearance.**
- **Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)**

☐ No changes
☐ New patent/exclusivity *(notify CDER OND IO)*
Date of check:

Note: If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.

❖ Actions	
• Proposed action • User Fee Goal Date is October 19, 2015	☒ AP ☐ TA ☐ CR
• Previous actions *(specify type and date for each action taken)*	☒ None
❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____	☐ Received
❖ Application Characteristics[3]	

[1] The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 2) lists the documents to be included in the Action Package.
[2] For resubmissions, 505(b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).
[3] Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA.

Review priority: ☐ Standard ☒ Priority
Chemical classification (new NDAs only):
(confirm chemical classification at time of approval)

☐ Fast Track
☒ Rolling Review
☒ Orphan drug designation
☒ Breakthrough Therapy designation
☐ Rx-to-OTC full switch
☐ Rx-to-OTC partial switch
☐ Direct-to-OTC

NDAs: Subpart H
☐ Accelerated approval (21 CFR 314.510)
☐ Restricted distribution (21 CFR 314.520)
Subpart I
☐ Approval based on animal studies

BLAs: Subpart E
☒ Accelerated approval (21 CFR 601.41)
☐ Restricted distribution (21 CFR 601.42)
Subpart H
☐ Approval based on animal studies

☐ Submitted in response to a PMR
☐ Submitted in response to a PMC
☐ Submitted in response to a Pediatric Written Request

REMS: ☐ MedGuide
☐ Communication Plan
☐ ETASU
☐ MedGuide w/o REMS
☒ REMS not required

Comments:

❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 *(approvals only)*	☐ Yes ☒ No
❖ Public communications *(approvals only)*	
• Office of Executive Programs (OEP) liaison has been notified of action	☐ Yes ☐ No
• Indicate what types (if any) of information were issued	☐ None ☒ FDA Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☒ Burst
❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity (orphan, 5-year NCE, 3-year, pediatric exclusivity)? • If so, specify the type	☐ No ☐ Yes
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	☐ Verified ☐ Not applicable because drug is an old antibiotic.

CONTENTS OF ACTION PACKAGE

Officer/Employee List

❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list *(approvals only)*	☒ Included
Documentation of consent/non-consent by officers/employees	☒ Included

Action Letters	
❖ Copies of all action letters *(including approval letter with final labeling)*	Approved on October 18, 2015
Labeling	
❖ Package Insert *(write submission/communication date at upper right of first page of PI)*	
• Most recent draft labeling *(if it is division-proposed labeling, it should be in track-changes format)*	☐ Included
• Original applicant-proposed labeling	☒ Included
❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling *(write submission/communication date at upper right of first page of each piece)*	☐ Medication Guide ☐ Patient Package Insert ☒ Instructions for Use ☐ Device Labeling ☐ None
• Most-recent draft labeling *(if it is division-proposed labeling, it should be in track-changes format)*	☒ Included
• Original applicant-proposed labeling	☒ Included
❖ Labels (**full color** carton and immediate-container labels) *(write submission/communication date on upper right of first page of each submission)*	
• Most-recent draft labeling	☒ Included
❖ Proprietary Name • Acceptability/non-acceptability letter(s) *(indicate date(s))* • Review(s) *(indicate date(s)*	Letter: 01/18/15 Review: 01/14/15
❖ Labeling reviews *(indicate dates of reviews)*	RPM: 05/01/15 DMEPA: 08/03/15 DMPP/PLT (DRISK): ☒ None OPDP: 10/15/15 SEALD: ☒ None CSS: ☒ None Product Quality ☒ None Other: Office of Biotechnology: 10/02/15
Administrative / Regulatory Documents	
❖ RPM Filing Review[4]/Memo of Filing Meeting *(indicate date of each review)* ❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee	04/20/15 ☒ Not a (b)(2)
❖ NDAs only: Exclusivity Summary *(signed by Division Director)*	☐ Included
❖ Application Integrity Policy (AIP) Status and Related Documents http://www fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
• Applicant is on the AIP	☐ Yes ☒ No

[4] Filing reviews for scientific disciplines are NOT required to be included in the action package.

• This application is on the AIP o If yes, Center Director's Exception for Review memo *(indicate date)* o If yes, OC clearance for approval *(indicate date of clearance communication)*	☐ Yes ☒ No ☐ Not an AP action
❖ Pediatrics *(approvals only)* • Date reviewed by PeRC N/A If PeRC review not necessary, explain: Orphan Designation	
❖ Breakthrough Therapy Designation	☐ N/A
• Breakthrough Therapy Designation Letter(s) (granted, denied, an/or rescinded)	Granted: 06/16/14
• CDER Medical Policy Council Breakthrough Therapy Designation Determination Review Template(s) *(include only the completed template(s) and not the meeting minutes)*	
• CDER Medical Policy Council Brief – Evaluating a Breakthrough Therapy Designation for Rescission Template(s) *(include only the completed template(s) and not the meeting minutes)* *(completed CDER MPC templates can be found in DARRTS as clinical reviews or on the MPC SharePoint Site)*	
❖ Outgoing communications: letters, emails, and faxes considered important to include in the action package by the reviewing office/division (e.g., clinical SPA letters, RTF letter, Formal Dispute Resolution Request decisional letters, etc.) *(do not include previous action letters, as these are located elsewhere in package)*	10/16/15, 10/15/15, 10/13/15, 10/06/15, 09/21/15, 09/17/15, 09/15/15, 08/05/15, 08/03/15, 07/30/15, 07/23/15, 07/15/15, 07/10/15, 06/16/15, 05/14/15, 04/20/15, 03/31/15, 03/04/15
❖ Internal documents: memoranda, telecons, emails, and other documents considered important to include in the action package by the reviewing office/division (e.g., Regulatory Briefing minutes, Medical Policy Council meeting minutes)	04/22/15
❖ Minutes of Meetings	
• If not the first review cycle, any end-of-review meeting *(indicate date of mtg)*	☒ N/A or no mtg
• Pre-NDA/BLA meeting *(indicate date of mtg)*	10/14/14
• EOP2 meeting *(indicate date of mtg)*	☒ No mtg
• Mid-cycle Communication *(indicate date of mtg)*	05/27/15
• Late-cycle Meeting *(indicate date of mtg)*	07/27/15
• Other milestone meetings (e.g., EOP2a, CMC focused milestone meetings) *(indicate dates of mtgs)*	
❖ Advisory Committee Meeting(s)	☒ No AC meeting
• Date(s) of Meeting(s)	
Decisional and Summary Memos	
❖ Office Director Decisional Memo *(indicate date for each review)*	10/16/15
Division Director Summary Review *(indicate date for each review)*	10/16/15
Cross-Discipline Team Leader Review *(indicate date for each review)*	10/15/15
PMR/PMC Development Templates *(indicate total number)*	☒ 1
Clinical	

❖ Clinical Reviews	
• Clinical Team Leader Review(s) *(indicate date for each review)*	☒ No separate review Cosigned 08/27/15 Review
• Clinical review(s) *(indicate date for each review)*	Review: 08/27/15
• Social scientist review(s) (if OTC drug) *(indicate date for each review)*	☒ None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here ☐ and include a review/memo explaining why not *(indicate date of review/memo)*	See 08/27/15 Clinical Review (pages 68-69)
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers *(indicate date of each review)*	Epidemiology Review: 09/15/15
❖ Controlled Substance Staff review(s) and Scheduling Recommendation *(indicate date of each review)*	☒ N/A
❖ Risk Management • REMS Documents and REMS Supporting Document *(indicate date(s) of submission(s))* • REMS Memo(s) and letter(s) *(indicate date(s))* • Risk management review(s) and recommendations (including those by OSE and CSS) *(indicate date of each review and indicate location/date if incorporated into another review)*	Review: 08/14/15
❖ OSI Clinical Inspection Review Summary(ies) *(include copies of OSI letters to investigators)*	
Clinical Microbiology ☒ None	
❖ Clinical Microbiology Team Leader Review(s) *(indicate date for each review)*	☐ No separate review
Clinical Microbiology Review(s) *(indicate date for each review)*	☐ None
Biostatistics ☒ None	
❖ Statistical Division Director Review(s) *(indicate date for each review)*	☐ No separate review
Statistical Team Leader Review(s) *(indicate date for each review)*	☐ No separate review
Statistical Review(s) *(indicate date for each review)*	☐ None
Clinical Pharmacology ☐ None	
❖ Clinical Pharmacology Division Director Review(s) *(indicate date for each review)*	☒ No separate review Cosigned 08/10/15 Review
Clinical Pharmacology Team Leader Review(s) *(indicate date for each review)*	☒ No separate review Pharmacometric cosigned 09/15/15 Review
Clinical Pharmacology review(s) *(indicate date for each review)*	Pharmacometric cosigned 9/15/15 Review: 08/10/15
❖ OSI Clinical Pharmacology Inspection Review Summary *(include copies of OSI letters)*	09/04/15, 09/03/15, 06/12/15

Nonclinical ☐ None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) *(indicate date for each review)*	10/01/15
• Supervisory Review(s) *(indicate date for each review)*	☒ No separate review Cosigned 07/20/15 (Primary) Review: 09/11/15 and 07/28/15 (Secondary) Review: 10/01/15 (Tertiary)
• Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	Reviews: 09/11/15 and 07/20/15 (Primary)
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer *(indicate date for each review)*	☒ None
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	☒ No carc
❖ ECAC/CAC report/memo of meeting	☒ None Included in P/T review, page
❖ OSI Nonclinical Inspection Review Summary *(include copies of OSI letters)*	☒ None requested
Product Quality ☐ None	
❖ Product Quality Discipline Reviews	
• Tertiary review (*indicate date for each review*)	☒ None
• Secondary review (e.g., Branch Chief) *(indicate date for each review)*	Cosigned 10/14/15
• Integrated Quality Assessment (contains the Executive Summary and the primary reviews from each product quality review discipline) *(indicate date for each review)*	Review: 10/14/15
❖ Reviews by other disciplines/divisions/Centers requested by product quality review team *(indicate date of each review):* Microbiology and Drug Substance	Drug Substance 07/21/15 Microbiology 07/19/15; Addendum 10/15/15
❖ Environmental Assessment (check one) (original and supplemental applications)	
☒ Categorical Exclusion *(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)*	See section S.7.1 of the 07/19/2015 CMC Microbiology Review
☐ Review & FONSI *(indicate date of review)*	
☐ Review & Environmental Impact Statement *(indicate date of each review)*	
❖ Facilities Review/Inspection	
☒ Facilities inspections (*action must be taken prior to the re-evaluation date*) *(only original applications and efficacy supplements that require a manufacturing facility inspection(e.g., new strength, manufacturing process, or manufacturing site change)*	☒ Acceptable Re-evaluation date: ☐ Withhold recommendation ☐ Not applicable

Day of Approval Activities	
❖ For all 505(b)(2) applications: • Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)	☐ No changes ☐ New patent/exclusivity *(Notify CDER OND IO)*
• Finalize 505(b)(2) assessment	☐ Done
❖ For Breakthrough Therapy (BT) Designated drugs: • Notify the CDER BT Program Manager	☐ Done *(Send email to CDER OND IO)*
❖ For products that need to be added to the flush list (generally opioids): Flush List • Notify the Division of Online Communications, Office of Communications	☐ Done
❖ Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email	☐ Done
❖ If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter	☒ Done
❖ Ensure that proprietary name, if any, and established name are listed in the *Application Product Names* section of DARRTS, and that the proprietary name is identified as the "preferred" name	☒ Done
❖ Ensure Pediatric Record is accurate	☐ Done
❖ Send approval email within one business day to CDER-APPROVALS	☒ Done

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/s/

ALYCIA C ANDERSON
10/19/2015

Anderson, Alycia

From: Anderson, Alycia
Sent: Friday, October 16, 2015 8:31 AM
To: dawn.collette@boehringer-ingelheim.com
Subject: FW: BLA 761025 - PI
Attachments: BLA761025 Draft Label PRAXBIND.4.3.docx

Dawn, I mean, today, Friday.

Alycia

From: Anderson, Alycia
Sent: Friday, October 16, 2015 8:27 AM
To: dawn.collette@boehringer-ingelheim.com
Subject: BLA 761025 - PI

Good morning, Dawn.

Please use this version of the label.

Attached is the PI for BLA 761025. Please review the changes/comments and do the following to the same draft:

- Accept any changes that you agree with and delete the comments that apply to those agreed upon changes
- Edit over the ones that you do not agree with (do not reject any changes that the FDA proposed)

After you have made the changes, feel free to send me the revised tracked change before you make your official submission electronically.

Please provide a revised PI to me by **10:00 a.m. (ET), Thursday, October 16, 2015.**

Best Regards,

Alycia Anderson
~~~~~~~~~~~~~~~
Alycia Anderson, CCRP
Regulatory Project Manager
CDER/OND/OHOP/DHP
10903 New Hampshire Avenue
WO #22, Room 2379
Silver Spring, MD 20903
(240) 402-4270 (Desk)
alycia.anderson@fda.hhs.gov

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/s/

ALYCIA C ANDERSON
10/16/2015

Anderson, Alycia

From: Anderson, Alycia
Sent: Thursday, October 15, 2015 1:53 PM
To: dawn.collette@boehringer-ingelheim.com
Subject: BLA 761025
Attachments: BLA761025 Draft label PRAXBIND.4.1.docx

Good morning, Dawn.

Please use this version of the label.

Attached is the PI for BLA 761025. Please review the changes/comments and do the following to the same draft:

- Accept any changes that you agree with and delete the comments that apply to those agreed upon changes
- Edit over the ones that you do not agree with (do not reject any changes that the FDA proposed)

After you have made the changes, feel free to send me the revised tracked change before you make your official submission electronically.

Please provide a revised PI to me by **4:00 p.m. (ET), Thursday, October 15, 2015.**

Best Regards,

Alycia Anderson
~~~~~~~~~~~~~~~
Alycia Anderson, CCRP
Regulatory Project Manager
CDER/OND/OHOP/DHP
10903 New Hampshire Avenue
WO #22, Room 2379
Silver Spring, MD 20903
(240) 402-4270 (Desk)
alycia.anderson@fda.hhs.gov

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/s/

ALYCIA C ANDERSON
10/15/2015

Anderson, Alycia

From: Anderson, Alycia
Sent: Tuesday, October 13, 2015 11:35 AM
To: dawn.collette@boehringer-ingelheim.com
Subject: BLA 761025 - PI
Attachments: BLA761025 Draft Label PRAXBIND.3.1docx.docx

Good morning, Dawn.

Please use this version of the label.

Attached is the PI for BLA 761025. Please review the changes/comments and do the following to the same draft:

- Accept any changes that you agree with and delete the comments that apply to those agreed upon changes
- Edit over the ones that you do not agree with (do not reject any changes that the FDA proposed)

After you have made the changes, feel free to send me the revised tracked change before you make your official submission electronically.

Please provide a revised PI to me by **COB, Tuesday, October 13, 2015.**

Best Regards,

Alycia Anderson
~~~~~~~~~~~~~~~
Alycia Anderson, CCRP
Regulatory Project Manager
CDER/OND/OHOP/DHP
10903 New Hampshire Avenue
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/s/

ALYCIA C ANDERSON
10/14/2015

Anderson, Alycia

From: Anderson, Alycia
Sent: Tuesday, October 06, 2015 2:45 PM
To: dawn.collette@boehringer-ingelheim.com
Subject: BLA 761025 - PI
Attachments: BLA761025 Draft Label PRAXBIND.2.3.2.CLIN.docx

Good afternoon, Dawn.

Please use this version of the label.

Attached is the PI for BLA 761025. Please review the changes/comments and do the following to the same draft:

- Accept any changes that you agree with and delete the comments that apply to those agreed upon changes
- Edit over the ones that you do not agree with (do not reject any changes that the FDA proposed)

After you have made the changes, feel free to send me the revised tracked change before you make your official submission electronically.

Please provide a revised PI to me by **3:00 p.m. (EST), Thursday, October 8, 2015.**

Best Regards,

Alycia Anderson
~~~~~~~~~~~~~~~
Alycia Anderson, CCRP
Regulatory Project Manager
CDER/OND/OHOP/DHP
10903 New Hampshire Avenue
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alycia.anderson@fda.hhs.gov

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/s/

ALYCIA C ANDERSON
10/08/2015

Anderson, Alycia

From: Anderson, Alycia
Sent: Thursday, September 17, 2015 11:03 AM
To: dawn.collette@boehringer-ingelheim.com
Cc: michelle.kliewer@boehringer-ingelheim.com
Subject: BLA 761025
Attachments: BLA761025DraftLabelPRAXBIND.2.2.docx

Good morning, Dawn.

Attached is the PI for BLA 761025. Please review the changes/comments and do the following to the same draft:

- Accept any changes that you agree with
- Edit over the ones that you do not agree with (do not reject any changes that the FDA proposed)

After you have made the changes, feel free to send me the revised tracked change before you make your official submission electronically.

Please provide a revised PI to me by **COB, Wednesday, September 23, 2015**

Best Regards,

Alycia Anderson
~~~~~~~~~~~~~~~
Alycia Anderson, CCRP
Regulatory Project Manager
CDER/OND/OHOP/DHP
10903 New Hampshire Avenue
WO #22, Room 2379
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alycia.anderson@fda.hhs.gov

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/s/

ALYCIA C ANDERSON
09/17/2015

Anderson, Alycia

From: Anderson, Alycia
Sent: Tuesday, September 15, 2015 6:21 AM
To: dawn.collette@boehringer-ingelheim.com
Subject: BLA 761025 - CMC IR

Good morning, Dawn. Our Chemistry, Manufacturing, and Controls Team has information that is being requested.

Please refer to your Biologics License Application (sBLA) dated February 20, 2015, received February 20, 2015, submitted under section 351(a) of the Public Health Service Act for Idarucizumab solution for injection/infusion (50 mg/mL).

We are reviewing your submission and have the following request for information.

1. Regarding DS and DP release and stability specifications:
    a. We do not agree with Boehringer Ingelheim's (BI) proposed plan for (b) (4) in lieu of acceptance criteria that are set based on the extent of clinical and manufacturing data presented. Additionally, many of BI's proposed acceptance criteria are not supported by the lot release data that was submitted in the BLA, nor by the more commonly used statistical methods for defining criteria based on the data available. (b) (4) Update the specifications for (b) (4) with the acceptance criteria that would align with criteria communicated by FDA on 28 July 2015 , which were based on the lot release and stability data presented in the BLA. Note that acceptance criteria can be changed post approval based on additional data that become available, for example, when sufficient lots are available for reassessment of criteria based on tolerance intervals and well defined critical quality attributes
    b. BI's proposed lower limit to the potency acceptance criterion is acceptable.
    c. The acceptance criterion for visible particles allows DP to contain (b) (4) . There was no information in the BLA supporting this acceptance criterion.
        i. Lot release information for DP lots used in the clinical trial state results as "pass" but does not provide any information that would enable FDA to identify whether any lot actually contained visible particles. Submit information for each lot used in your clinical studies on whether the lot did or did not present with (b) (4) in order to enable assessment of patient exposure to DP containing these particles. For lots that contained these particles, identify how many particles were present in each of the vials tested.
        ii. The BLA did not include information on any quantitative limits for (b) (4) . Identify the limits that defined (b) (4) , and identify how quantitation of the particles is done.
        iii. The BLA did not contain any characterization of the (b) (4) . Submit data from analysis of these particles to support that the particles are made up from idarucizumab.
        iv. Address whether formation of these particles are initiated by (b) (4) . and identify any corrective/preventive actions that would reduce these visible particles (b) (4) .

2 The BLA eCTD sections 3.2.P.3.3 and 3.2.P.3.4 should reflect the manufacturing and control process that has been developed and validated for idarucizumab, including specific informaiton on critical equipment used, a sufficiently

detailed description of each process steps, and limits based on the development and validation studies. Although BI has provided more extensive descriptions of the manufacturing process under the Manufacturing Process Development section 3.2.P.2 and in the process validation section 3.2.P.3.5., as well as in a number of responses to information requests, sections 3.2.P.3.3 and 3.2.P.3.4 do not include much of the significant information that would be required to define the idarucizumab process. Update sections 3.2.P.3.3 and 3.2.P.3.4 with comprehensive information about the idarucizumab DP manufacturing process. Examples of the type of information that should be included are identified below, although this is not necessarily a comprehensive list of all information that should be included in these sections.

a. (b) (4): maximum hold time and temperature for this step, maximum duration of (b) (4)

b. (b) (4)

   i. Your manufacturing process allows (b) (4). Section 3.2.P.3.3.3.11 does not define how your numbering and traceability of the lots are implemented to ensure identification of the (b) (4) Moreover, neither section 3.2.P.3.3 nor section 3.2.S.2.2 specifies how the maximum storage time is controlled for these lots. For example, specific maximum hold times at various conditions were defined based on data presented, and a specific expiration dating will be set for DS lots. The BLA does not address how DS expiration dating, maximum hold times, etc. will be specified for lots (b) (4). This information should be included in sections 3.2.P.3.3 and section 3.2.S.2.2, as relevant.

   ii. The procedure for (b) (4) as supported by the validation studies.

c. (b) (4) identify the vessel into which (b) (4) and specify the temperature(s) and maximum hold times (b) (4).

d. Filling : (b) (4) as defined based on the validated process.

   i. The (b) (4) is identified as a critical parameter (b) (4). Information for this process should include, but not be limited to: (b) (4) The process undertaken when (b) (4) criteria are not met and any other relvant parameter that assures (b) (4) accuracy

e. (b) (4) This was identified as "critical" and development information identified this parameter as (b) (4) mm, but sections 3.2.P.3.3. and 3.2.3.4 only state that verification of (b) (4) should be done. update these sections with the numerical process limits for the (b) (4)

f. In BI's June 26-2015 response to the FDA's June-16-2015 information request, the sampling plan for filled vials was described. This should be updated in Section 3.2.P.3.3.

g. Hold Times: update the sections with maximum validated hold times and temperatures for the different steps in the DP manufacturing process.

h. Secondary Packaging: In Section 3.2.P.3.3.3.8 for secondary packaging, your paragraph on identification and differentiation of idarucizumab from other products does not specify the identifier (s) used. This paragraph only states that (b) (4) Update this section of the BLA with the specific identity parameter used for idarucizumab.

3 Section 3.S.2.2.3.11 states that (b) (4) It is not clear whether any of the stability data provided in support of expiration dating was from idarucizumab (b) (4). Provide information on any of the lots for which we have stability data to support expiration dating that may be relevant to these processes. Update the BLA sections 3.2.S.2.2 and 3.2.P.3.3 with the process for which you have stability data. Any (b) (4) activities can be licensed through a supplement with supporting information.

4 Section 3.2.P.3.5.3 states that [redacted] In BI's June 26, 2015 response to the FDA's June 16, 2015 information request, results of the validation for the [redacted] were provided. Update Section 3.2.P.3.5.3 to reflect these validated volumes. Until such time as the results of the validation studies are submitted to the FDA, lots manufactured using [redacted] should not be released to the U.S. market.

5 In BI's August 12 2015 response to an FDA Information Request FDA asking that BLA sections 3.2.S.2.1, 3.2.P.3.1, and forms356h be updated with specific information regarding the activities done at each manufacturing site, BI stated that only form 356h was updated. Update the relevant manufacturer's sections in sections 3.2.S and 3.2.P with the detailed information, including the validated activities/testing done at each site.

6 An Information Request sent on August 3 2015 asked that BI set a maximum time for [redacted] across the entire DP manufacturing process. In BI's response (August 7 2015), BI replied that [redacted] is controlled by [redacted]. This strategy is not acceptable. Update the BLA with the validated cumulative time limit for [redacted] during DP manufacture, and reference or provide the data which is the basis for this validated time.

7 For the [redacted] steps referenced in 3.2.P.3.2 and the cross referenced to 3.2.S.2.2, the FDA could not find descriptions in the Batch Record. Therefore, please identify where this information can be found. If these steps are controlled by a protocol rather than in the Batch Record, identify where in the Batch Record there is a specific reference to this protocol , and submit the protocol to the BLA. This protocol should contain, but not be limited to [redacted].

8 Validation 3.2.P.5.5.1 – states tha [redacted] ." Note that a change in lot size outside of the validated range will require FDA approval.

9 Section 3.2.P.3.5.5 states that "This section describes the validation of idarucizumab drug product manufacture in the fill and finish area [redacted], while Table 1 in section 3.2.P.3.5 identifies the DP filling facility as [redacted]. Please clarify the differences [redacted].

10 For assessment of [redacted] in section 3.2.P.2.3.2.7, provide a list of leachables observed in analysis of the [redacted]. Additionally, provide any data or rationale for your statement that these leachables are not of toxicological concern

11 Please explain and reconcile the difference between [redacted] and [redacted] " stated in the Drug Process Validation Section 3.2.P.3.5. Section 3.2.P.3.5.1 states that [redacted] at Boehringer-Ingelheim, while section 3.2.P.3.5.2 states that [redacted].

Please provide a written response to the above information request, **by COB, Monday, September 21, 2015**. Please formally submit your information to the BLA.

Please inform me of receipt of this e-mail.

Best Regards,

Alycia Anderson
~~~~~~~~~~~~~~~
Alycia Anderson, CCRP
Regulatory Project Manager
CDER/OND/OHOP/DHP
10903 New Hampshire Avenue
WO #22, Room 2379
Silver Spring, MD 20903
(240) 402-4270 (Desk)
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/s/

ALYCIA C ANDERSON
09/15/2015

Anderson, Alycia

From: Anderson, Alycia
Sent: Friday, August 14, 2015 6:08 AM
To: dawn.collette@boehringer-ingelheim.com
Subject: BLA 761025 - IR

Good morning, Dawn. Our Office of Biotechnology Products

We have the following comments regarding your proposed container labels and carton labeling submitted on August 12, 2015.

Container Label and Carton Labeling

1. Delete the trailing zeroes from the quantity of "polysorbate 20 (10.00 mg)" so that it appears as "polysorbate 20 (10 mg)". Trailing zeroes appear on the Institute of Safe Medication Practice's List of Error-Prone Abbreviations, Symbols, and Dose Designations[1]. As part of a national campaign to avoid the use of dangerous abbreviations and dose designations, FDA agreed not to approve such error prone text in the approved labeling of products.

2. Add the units of measure to the temperature range in the storage statement so that it appears as "2°C to 8°C (36°F to 46°F)".

Please provide a written response to the above information request, **by COB, Wednesday, August 19, 2015**. Please formally submit this information to the IND.

Please inform me of receipt of this e-mail.

Best Regards,

Alycia Anderson
~~~~~~~~~~~~~~~
Alycia Anderson, CCRP
Regulatory Project Manager
CDER/OND/OHOP/DHP
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Silver Spring, MD 20903
(240) 402-4270 (Desk)
alycia.anderson@fda.hhs.gov
~~~~~~~~~~~~~~~

[1] ISMP's List of Error-Prone Abbreviations, Symbols, and Dose Designations [internet]. Horsham (PA): Institute for Safe Medication Practices. 2013 [cited 2015 August 13]. Available from: http://www.ismp.org/tools/errorproneabbreviations.pdf.

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/s/

ALYCIA C ANDERSON
08/14/2015

Anderson, Alycia

From: Anderson, Alycia
Sent: Wednesday, August 05, 2015 3:06 PM
To: dawn.collette@boehringer-ingelheim.com
Subject: BLA 761025 - IR

Good afternoon, Dawn. Our Division of Medication Error Prevention and Analysis and the Office of Biotechnology Products

We have the following comments regarding your proposed container labels, carton labeling, (b) (4) submitted on February 20, 2015 and May 29, 2015.

A. General Comments

1. Confirm there is no text on the ferrule and cap overseal of the vials to comply with USP General Chapters: <7> Labeling, Labels and Labeling for Injectable Products, Ferrules and Cap Overseals.

2. Indicate how the label is affixed to the vial and where the visual area of inspection is located per 21 CFR 610.60(e).

B. Carton Labeling

1. Ensure the font size of the proper name "idarucizumab" is at least half the size of the proprietary name and has prominence commensurate as per 21 CFR 201.10(g)(2).

2. Remove (b) (4) as this is intervening matter per 21 CFR 201.10(a).

3. Relocate the dosage form "Injection" to appear below the proper name. For CDER-regulated the proper name for CDER-regulated biological products should not include the finished dosage form. The finished dosage form, Injection, can appear on the line below the proper name.[1]

4. Revise the strength statement such that the strength per total volume is more prominent than the strength per mL by decreasing the font and relocating the strength per mL (50 mg/mL) to appear immediately under the strength per total volume (2.5 g/50 mL) wherever presented on the labels and labeling per USP General Chapters <1>.

5. Remove the statement (b) (4) to avoid misinterpretation that this product (b) (4) and relocate the statement "For Intravenous Use Only" in its place to ensure adequate prominence of the route of administration.

6. Place the following statement under the "For Intravenous Use Only":
"For Single Use Only. Discard Unused Portion"

7. Decrease prominence of Rx only and relocating to the upper right portion of the principal display panel (PDP) where "FOR INTRAVENOUS USE ONLY" appears.

8. Revise all statements of (b) (4) to the following: "Administer 2 vials for complete dose of 5 g".

9. Revise the net quantity statement to "Net quantity - Contains 2 vials each containing 2.5 g/50 mL". Thus, the PDP should appear as:

Praxbind
idarucizumab
Injection

2.5 g/50 mL
(50 mg/mL)

For Intravenous Use Only
Single-Use Only, Discard Unused Portion
Administer 2 vials for complete dose of 5 g
Net quantity- Contains 2 vials each containing 2.5 g/50 mL

10. Revise the dosage statement to the following:
For single use only. See package insert for Full Prescribing Information for dosage and administration. Discard unused portion.

11. Revise the list of ingredients to include the amounts and place in alphabetical order to comply with USP <1051> Labeling of Inactive Ingredients. The statement should appear as:
Each 50 mL vial contains 2.5 g of idarucizumab, acetic acid glacial (x mg), polysorbate 20 (x mg), sodium acetate trihydrate (x mg), sorbitol (x mg) and water for injection.

12. Add the statement "No U.S. standard of potency" near the list of ingredients to comply with 21 CFR 610.61(r)

13. Delete "(b) (4)". This product will only be administered in a clinical setting.

14. Revise the statements (b) (4) statements on the top panel where the lot number and expiration date is located to the following:
Administer 2 vials for complete dose of 5 g
See package insert for Full Prescribing Information for dosage and administration.

15. Revise the statements (b) (4) on the opening flap inside panel to the following:
See package insert for Full Prescribing Information for dosage and administration and Administer 2 vials for complete dose of 5 g

16. Delete the following statements from the opening flap inside panel:
(b) (4)

17. The Applicant/Licensee on the 356h form is the manufacturer per 21 CFR 600.3(t). The Applicant must appear as "Manufactured by:". Additionally, the U.S. License Number must appear with the manufacturer information per 21 CFR 610.61(b). Revise the manufacturer information to appear as:
Manufactured by:
Boehringer Ingelheim Pharmaceuticals, Inc.
Ridgefield, CT 06877

U.S. License Number 2006

Currently the proposed labeling lists the Applicant as the distributor and states (b) (4) If you propose to include this information on the labeling, cite the regulations you are attempting to fulfill.

C. Vial Container Label

1. See comments B1, B2, B3, B4, B5, B6, B7, B8, B10, and B11.

2. Revise the orientation of the side panel so that it is displayed horizontally[1].

3. See comment B17. For the vial container label, only the Applicant/Licensee information is required. Consider omitting any additional manufacturer information.

(b) (4)

Please provide a written response to the above information request, **by COB, Tuesday, August 11, 2015**. Please formally submit this information to the IND.

Please inform me of receipt of this e-mail.

Best Regards,

Alycia Anderson
~~~~~~~~~~~~~~~

Alycia Anderson, CCRP
~~~~~~~~~~~~~~~

Regulatory Project Manager
CDER/OND/OHOP/DHP
10903 New Hampshire Avenue
WO #22, Room 2379
Silver Spring, MD 20903
(240) 402-4270 (Desk)
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[1] See Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. 2013 April. Available from: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf.

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/s/

ALYCIA C ANDERSON
08/05/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 761025

INFORMATION REQUEST

Boehringer Ingelheim Pharmaceuticals, Inc.
Attention: Michelle Kliewer, RN, RAC
Director, Regulatory Affairs
900 Ridgebury Road
P.O. Box 368
Ridgefield, CT 06877

Dear Ms. Kliewer:

Please refer to your Biologics License Application (sBLA) dated February 20, 2015, received February 20, 2015, submitted under section 351(a) of the Public Health Service Act for Idarucizumab solution for injection/infusion (50 mg/mL).

We are reviewing your submission and have the following request for information. We request a response by August 7, 2015 in order to continue our evaluation of your application.

Information request regarding DP manufacturing

1. We acknowledge your protocols for validation of [redacted] (b) (4) that were provided in your July 15, 2015 responses to the FDA. Until these studies have been completed and reviewed by the FDA, Drug Product manufacturing should only be performed using [redacted] (b) (4) As part of this response, you will also need to provide information on [redacted] (b) (4)

2. In order to help understand the impact of [redacted] (b) (4) identify whether the lot was manufactured from [redacted] (b) (4).

3. We acknowledge your protocols for validation of [redacted] (b) (4) that you have provided in your June 26, 2015 responses to the FDA. We also note that there is an [redacted] (b) (4) (page 259 of your response). [redacted] (b) (4) Indicate if [redacted] (b) (4) in the drug product manufacturing process. Any [redacted] (b) (4) steps in the drug product manufacturing process should be clearly identified in section 3.2.P.3.3, including descriptions of the conditions under which [redacted] (b) (4) would occur, [redacted] (b) (4)

[redacted] etc. Adequate justification for these control parameters and timelines should be provided. Additionally, you should also identify in the BLA that successful results of the [redacted] validation protocols will be submitted in an annual report.

4. Regarding determination of process capability of the filling process, the significance of your Cp and and Cpk assessment needs to be fully explained. Cp and Cpk values appear to be within the specified ranges of PV target Criteria/ PV acceptance criteria [redacted], except for DP lot 306693, which appears to have lower values. It therefore appears that this lot did not meet acceptance criteria. Provide a justification or explanation to support that lot 306693 was within the expected process capability.

5. Section 3.2.p.3.3 states that you intend to manufacture DP [redacted]. Validation information provided shows [redacted]. Therefore, section 3.2.p.3.3 should be updated to include [redacted].

6. In order to control for [redacted] during Drug Product manufacturing you should provide adequate assurance that your proposed maximum overall [redacted] will allow Drug Product to maintain specified Quality Attributes throughout your proposed storage time for Drug Product. This would include the [redacted] which is defined as [redacted] days.

7. Polysorbate 20 [redacted] Describe your storage and control procedures for polysorbate 20 that ensure the maintenance of the polysorbate 20 quality.

8. From your July 15, 2015 response to our IR #10, we see that for [redacted] testing sites, many of the assays have not been transferred or validated at these sites as of this BLA timeline. Therefore, these sites, or the specific assays for which assay transfer validation reports have not yet been submitted to the BLA, will have to be removed from the BLA. Testing activities at these sites can be added to the license through submission of the required information in a supplement once assay transfer qualification/validation activities have been finalized.

9. For information on [redacted] process validation (3.2.P.3.5):
   a. Submit the [redacted] microbial retention study report completed by [redacted]. The report should include controls, acceptance criteria, incubation conditions [redacted] viability of the challenge organism.
   b. Submit the validation report for the [redacted] integrity test. Be sure to include the following information:
      i. [redacted]

ii. (b) (4)

iii. (b) (4)

If you have questions, call Melinda Bauerlien, Regulatory Business Process Manager at (301) 796-0906.

Sincerely,

Chana Fuchs -S

Digitally signed by Chana Fuchs -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Chana Fuchs -S, 0.9.2342.19200300.100.1.1=2000601863
Date: 2015.08.03 09:55:55 -04'00'

Chana Fuchs, Ph.D.
Team Lead
Division of Biotechnology Research and Review IV
Office of Biotechnology Products
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

Anderson, Alycia

From: Anderson, Alycia
Sent: Thursday, July 30, 2015 2:24 PM
To: dawn.collette@boehringer-ingelheim.com
Cc: michelle.kliewer@boehringer-ingelheim.com
Subject: BLA 761025
Attachments: BLA761025 Draft label PRAXBIND.FDA.1.docx

Good afternoon, Dawn.

Attached is the PI for BLA 761025. Please review the changes/comments and do the following to the same draft:

- Accept any changes that you agree with
- Edit over the ones that you do not agree with (do not reject any changes that the FDA proposed)

After you have made the changes, feel free to send me the revised tracked change before you make your official submission electronically.

Please provide a revised PI to me by **11:00 a.m. (ET), Thursday, August 6, 2015**.

Best Regards,

Alycia Anderson
~~~~~~~~~~~~~~~
Alycia Anderson, CCRP
Regulatory Project Manager
CDER/OND/OHOP/DHP
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Silver Spring, MD 20903
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7 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page
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/s/

ALYCIA C ANDERSON
07/30/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 761025

INFORMATION REQUEST

Boehringer Ingelheim Pharmaceuticals, Inc.
Attention: Michelle Kliewer, RN, RAC
Director, Regulatory Affairs
900 Ridgebury Road
P.O. Box 368
Ridgefield, CT 06877

Dear Ms. Kliewer:

Please refer to your Biologics License Application (sBLA) dated February 20, 2015, received February 20, 2015, submitted under section 351(a) of the Public Health Service Act for Idarucizumab solution for injection/infusion (50 mg/mL).

We are reviewing your submission and have the following request for information. We request a written response by July 30, 2015 in order to continue our evaluation of your application.

1. Please clarify for the (b) (4)

2. Indicate when the (b) (4) qualification report using samples from two additional batches will be submitted to the Agency

3. Submit endotoxin limits of (b) (4) purification steps

4. Indicate when the study report for the maximum hold times of (b) (4) from microbiology perspective will be submitted to the Agency.

5. It is noted that due to your current (b) (4)

   Study reports for the qualification of (b) (4) method and hold time validation can be submitted in the next Annual Report.

If you have questions, call Melinda Bauerlien, Regulatory Business Process Manager at (301) 796-0906.

Sincerely,

Chana Fuchs -S

Digitally s gned by Chana Fuchs S
DN: c=US o=U S Government ou=HHS ou=FDA ou=People cn=Chana Fuchs S 0 9 2342 19200300 100 1 1=2000601863
Date: 2015 07 23 11:33:33 04 00

Chana Fuchs, Ph.D.
Team Lead
Division of Biotechnology Research and Review IV
Office of Biotechnology Products
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

Anderson, Alycia

From: Anderson, Alycia
Sent: Friday, July 10, 2015 8:06 AM
To: dawn.collette@boehringer-ingelheim.com
Cc: Fuchs, Chana
Subject: BLA 761025 - IR

Good morning, Dawn. Our Office of Biotechnology Products has information that is being requested.

Please refer to your Biologics License Application (sBLA) dated February 20, 2015, received February 20, 2015, submitted under section 351(a) of the Public Health Service Act for Idarucizumab solution for injection/infusion (50 mg/mL).

We are reviewing your submission and have the following request for information.

1. In reference to the information submitted on June 26, 2015 in response to FDA's information request of June 16, 2015, we have the following requests for clarification and additional information:
   a. Regarding Question 5: the approach to evaluate the stability of the MCB does not appear sufficient for providing assurance that (b) (4).
   In your response, you indicate that in the event that (b) (4) This would not ensure (b) (4) The stability protocol should be updated to address this point, for example, include that (b) (4) Additionally, your protocol should identify an alert limit (b) (4) Provide the updated information to MCB2 stability protocol in your response, and submit the MCB2 stability protocol with your response.

   b. Regarding your response to our question 12 from the June 16, 2015 IR:

      i. From the updated flow diagrams provided in the response, it appears that a number of parameters having the potential to affect consistency in manufacturing and ultimately quality of the product are listed as in-process controls and do not include limits.
      We understand from the definitions provided in table 1 of section 3.2.S.2.4 that (b) (4) In line with these definitions, the monitoring of (b) (4) is appropriate given that these parameters can be adjusted in real time to ensure consistency of the process when not meeting defined ranges. However, (b) (4) are parameters that need to be controlled by limits since exceeding these limits would directly impact the ability to initiate the next step as well as consistency of the process, and product quality.

Update section 3.2.S.2.2 to include [redacted] as in-process controls and update section 3.2.S.2.4 to include IPC process limits for these parameters.
For the purification process, limits should also be included for yield.

ii. We note that [redacted] which are listed as being monitored in section 3.2.S.2.2 are not included in the batch records. Please clarify the absence of monitoring for these parameters as reflected in the batch records provided. We also note that [redacted] is listed as a parameter in the batch records. Please define the parameter.

c. Question 13 from the June 16, 2015 IR: From the information in the BLA and your response to our IR 13 regarding the qualification of new primary or working RS, we are unable to review and determine whether your process for qualification of a new RS is acceptable because we do not have the full information needed.

i. Your response is very general, and not clear about many of the parameters identified for the particular purpose of RS qualification. For example, for $\%CV_{HIST}$ you identify examples of method control charts or validation experiments without a clear definition of what is specified to be used for the purpose of qualification of a new RS. Additionally, the reply is confusing because qualification and requalification of RS are not well differentiated, and we do not understand whether your RS stored at each condition is stable as you have not provided these data, etc. These are examples of some of the information items that are lacking or unclear in your submitted material regarding new RS qualification and existing RS requalification.
ii. In your response, submit the full protocols for qualification of a new reference standard and for requalification of an existing RS
iii. Include all available stability data for your reference standards stored under the different conditions identified.
iv. In your response to our IR 13.b)i you indicate that the revised acceptance criteria for the thrombin clotting assay and the Fab binding activity assay (SPR) are [redacted]% and [redacted]%, respectively, and state that the numbers [redacted]. It is not clear that this is acceptable or if it is, how this would be done in an appropriate manner so as to ensure the maintenance of acceptable criteria such that the criteria are not negatively impacted by cumulative changes occurring in the historical RS. Please identify the parameters, including formulas, datapoints , criteria and controls to be included [redacted] so that you can assure that these adjustments do not allow drift. This should be addressed for qualification of new RS as well as for requalification of existing RS.
v. In your response to IR 13.b)ii, regarding the assignment of a potency of [redacted]%, you state that [redacted]. While the use of [redacted] may be acceptable under certain conditions, you have not defined the conditions and rules for [redacted]. Provide the full protocol, including relevant and detailed description of the conditions, rules, formulas, factors, etc. under which a [redacted] would be used and how [redacted] would be determined, as well as a comprehensive explanation on how your rules, criteria, formula, etc. would ensure that potency is maintained as reflective of the clinical material used to define safety and efficacy of idarucizumab and to prevent drift.

2. Regarding Pharmaceutical Development, document 2618129-p200al0101:
a. From pages 40-42 of the specified document, regarding extractables studies on [redacted] rubber stoppers, your finding that [redacted] extracts of the stoppers contain no semi-volatile or non-volatile compounds provides reassurance of stopper safety, since the DP is formulated in [redacted]. However, the [redacted]

(b) (4) Therefore, in order to provide adequate support for stopper safety, you should provide a tabulation of the levels of all the compounds found in (b) (4) extracts, together with adequate justification that these compounds do not pose safety concerns at the observed levels.

b. Regarding in use compatibility studies , pp. 43-44 : When used in clinical settings, your product will be exposed to a number of different materials that may interact and affect its safety and efficacy. You have provided a statement that (b) (4) In order for the Agency to adequately assess this statement and the instructions in the package insert, provide summary data for the measurements of (b) (4) and quality attributes from these studies. Please provide these data in a tabulated format.

3. We note that testing of the Master Cell Bank (MCB) was performed per 9CFR for bovine viruses. Confirm that the testing for porcine viruses was also performed per 9 CFR requirements.

4. For the (b) (4) validation runs, provide (b) (4) data (b) (4) .

5. In section 3.2.S.2.5 (chapter 5), reference is made to the (b) (4) Provide the parameters for the (b) (4) used and data for these studies.

6. You have proposed a (b) (4) month shelf life for the Idarucizumab Drug Substance. Your licensing submission contains real time stability data extending through a maximum of 12 months. Update the BLA with results from all lots that are on stability, including any lots from processes (b) (4)

7. We note that while the stress stability studies described in section 3.2.S.7 include three batches manufactured in November 2014 using the CMC3 final manufacturing process, the long term, mid-term and accelerated stability studies do not include any batches manufactured using the CMC3 final commercial process. Identify the CMC3 batches on stability and provide available data supporting the stability under the long term, mid-term and accelerated conditions for batches manufactured using the CMC3 final commercial process.

8. In section 3.2.A.2, table 19, the footnotes indicate that (b) (4) Please identify the number of cycles (b) (4) of the study.

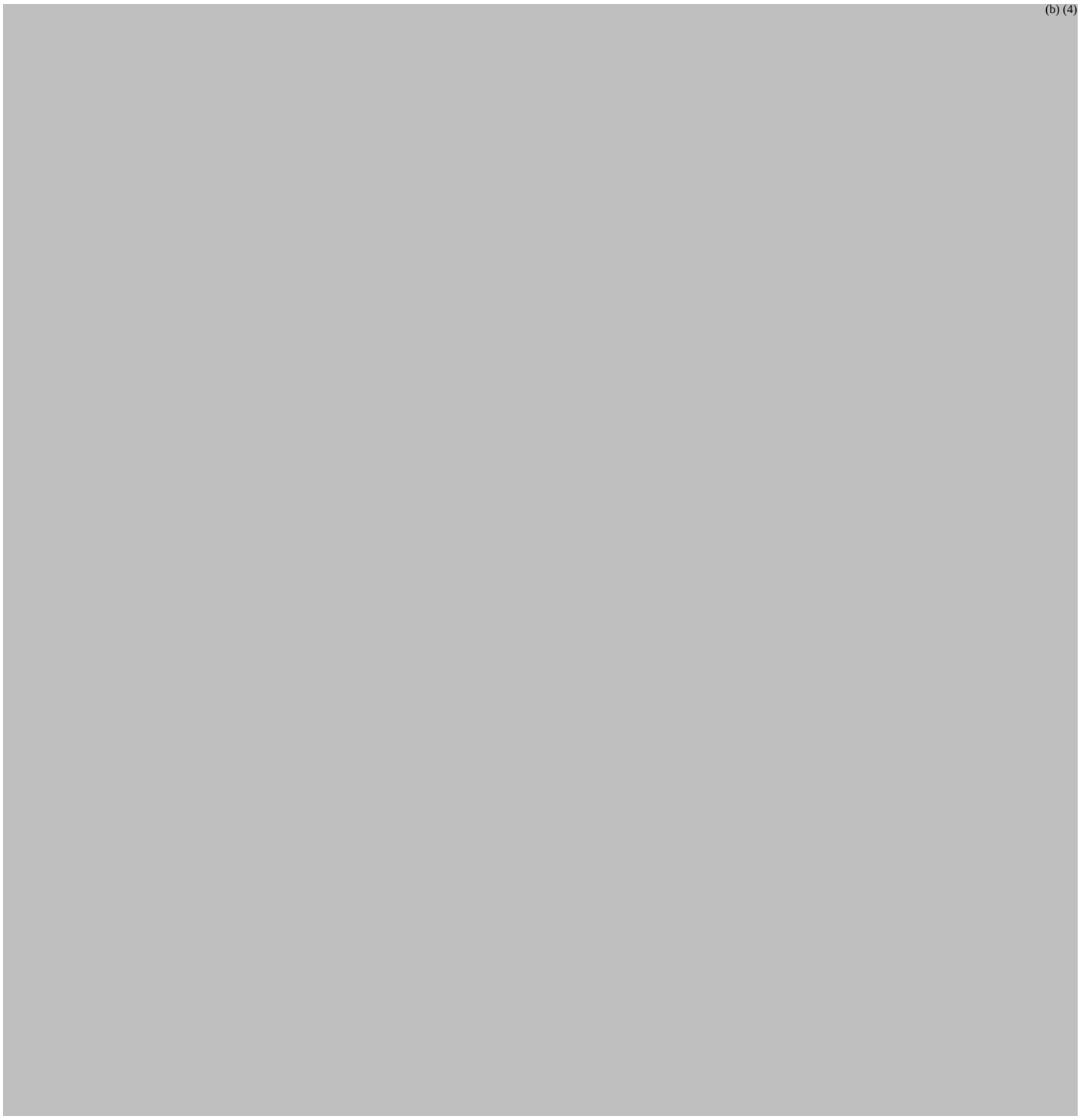
9. Under the description of the protective properties of the container closure suitability in section 3.2.S.6, reference is made to a photosensitivity study included in section 3.2.S.7.3.1; however, the study is not included in the above-referenced section. Update the BLA with this information.

10. It is not clear that all lot release and stability tests are implemented at each site where lot release and stability testing is specified in form 356h and sections 3.2.S.2.1 and 3.2.P.3.1. Update the BLA with the specific tests to be implemented at each site, and for each site and assay, refer to the validation or assay transfer qualification study that were used to ensure that the assay used at the site is within the validated state, and identify where the relevant transfer qualification study can be found in the BLA.

11. Regarding the annual stability testing of drug substance, the recommended DS storage temperature of (b) (4) °C (b) (4) idarucizumab that would allow identification of any changes in stability due to unanticipated causes that would be identified through stability monitoring. The inclusion of accelerated stability conditions at (b) (4) °C as part of annual stability monitoring would be expected to identify some such events, however it is not clear that the (b) months timeline specified would be sufficient for that purpose considering the stability profiles identified in the

BLA. Therefore, the timeline for the annual stability lot stored at (b) °C should be extended. Update section 3.2.S.7.2 with the revised stability protocol.

12. Update section 3.2.S.2.2 to include the following process parameters and operating ranges/acceptance criteria and submit the updated section in your response:



13. Section 3.2.P.3.3 Description of Manufacturing Process and Process Controls, Table 4 "Idarucizumab (b) (4) appears to summarize (b) (4). Please provide a description of the (b) (4) for the drug product manufacturing process.
14. Please amend section 3.2.P.3.4 Control of Critical Steps (b) (4) to include descriptions of the analytical methods used to measure (b) (4) bioburden and endotoxin.
15. Address the following points related to section 3.2.P.3.5 Process Validation and/or Evaluation:

a. Provide the [redacted] run. Specifically, the duration from [redacted]. Include definitions of the start and end time points.
b. Submit the study reports for the [redacted] studies completed during the initial qualification studies for [redacted]. Include identification of the source of the endotoxin used in the study.
c. With regard to media fill, provide the dates for the current media fill data submitted in the BLA (Batches 301033, 305591, 401000, and 406043).
d. Define the start and end time for the fill durations used during media fills.
e. Provide actions taken in the event of a media fill failure.
f. With regard to the transport validation studies, please describe the monitoring points at which temperature data was collected.
g. Provide a description and/or a diagram showing the location of the [redacted]
h. Provide acceptance criteria for the transport validation studies.

16. Provide a comprehensive list of all the protocols included in the submission that are intended to be approved with the BLA. We have identified many protocols in the BLA, for example, the protocols for [redacted] process validation studies, annual stability studies for DS and DP, [redacted] etc. These and the other protocols that are in the BLA should be included in this list.
17. The BLA includes a number of commitments for future activities, either submitted as part of the BLA or included in response to our information requests. Provide a comprehensive list of commitments for future activities that are included in the BLA, as well as BI's plans for updating the BLA for each of these.
18. At this point in the review timeline, please provide updates to the BLA for all sections which were updated through the various IR responses, including responses from this IR, so we can identify any remaining deficiencies and address them in a timely manner.

If you have questions, call Melinda Bauerlien, Regulatory Business Process Manager at (301) 796-0906.

Please provide a written response to the above information request, **by 12:00 p.m. (ET), Wednesday, July 15, 2015**. When replying to this IR, please reply to all.

Please confirm receipt of this e-mail.

Best Regards,

Alycia Anderson
~~~~~~~~~~~~~~~
Alycia Anderson, CCRP
Regulatory Project Manager
CDER/OND/OHOP/DHP
10903 New Hampshire Avenue
WO #22, Room 2379
Silver Spring, MD 20903
(240) 402-4270 (Desk)
alycia.anderson@fda.hhs.gov
~~~~~~~~~~~~~~~

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ALYCIA C ANDERSON
07/10/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 761025

INFORMATION REQUEST

Boehringer Ingelheim Pharmaceuticals, Inc.
Attention: Michelle Kliewer, RN, RAC
Director, Regulatory Affairs
900 Ridgebury Road
P.O. Box 368
Ridgefield, CT 06877

Dear Ms. Kliewer:

Please refer to your Biologics License Application (sBLA) dated February 20, 2015, received February 20, 2015, submitted under section 351(a) of the Public Health Service Act for Idarucizumab solution for injection/infusion (50 mg/mL).

We are reviewing your submission and have the following request for information. We request a written response by June 26, 2015 in order to continue our evaluation of your application.

1. In reference to the information submitted on Jun 4, 2015 in response to FDA's information request of May 14, 2015, we have the following requests for clarification and additional information:

   a. With regards to your response to question 1.a, clarify if samples (b) (4) .

   b. The hold and storage times shown in Table 1 of your response to question 1.b are (b) (4) that was in the BLA. Please provide data justifying the (b) (4)

   c. With regard to your response to question 2.f, qualify (b) (4) samples using two additional runs.

   d. With regard to your response to question 2.i, justify how endotoxin levels of (b) (4) EU/mL are appropriate (b) (4) . In addition, it is not clear if the (b) (4) step is able to lower endotoxin levels from (b) (4) EU/mL to (b) (4) EU/mL during the (b) (4) .

   e. With regard to your response to question 2.j, include a product positive control in the (b) (4) testing as indicated in USP <85>.

f. [redacted] (b) (4)

2. In Sections 3.2.S.4.3 and 3.2.P.5.3 *Validation of Analytical Procedures*, for all compendial methods except for endotoxin and bioburden assays used for idarucizumab drug substance and drug product release and stability testing, limited information (e.g., osmolality) or no information (all other methods) was provided to show that product specific matrix does not interfere with the method. Submit relevant data to demonstrate that the following compendial methods are suitable for intended use for idarucizumab drug substance and/or drug product testing: appearance (including degree of coloration and clarity, degree of opalescence and visible particles), pH, osmolality, subvisible particles and sterility.

3. In Section 2.5 *Clinical Overview*, you mentioned that a modified thrombin time assay was used for possible formation of anti-dabigatran antibodies. However, no information was found with regard to the method description, standard operating procedure, method validation protocol, and method validation report. Provide this information to the BLA or provide the location of such information if it has already been submitted.

4. Section 3.2.S.2.3.3 states that if additional working cell banks (WCBs) are needed, [redacted] (b) (4) The protocol(s) for manufacturing and qualification of a new WCB should be submitted to the BLA for approval. If a protocol is not submitted at this time, clarify in the BLA that implementation of any future WCB will be submitted as a prior approval supplement (PAS); the WCB protocol could also be submitted as a PAS for prior approval and reduction of subsequent reporting categories when new WCBs are implemented. Qualification of a new WCB should include, but not be limited to, analyses of growth characteristics, productivity, viability, and product quality attributes, and the protocol should include manufacturing of commercial scale lots and putting initial lot(s) on stability.

5. The proposed approach to evaluate the stability of the MCB is not appropriate. In section 3.2.S.2.3 you specify that [redacted] (b) (4)

herefore, a protocol for testing the stability of MCB2 should be developed. Based on existing data and supporting information that will be generated from the current WCB, Submit the updated protocol for evaluation of MCB2 stability.

6. We note that regarding validation of the step, differences were observed for (batches 10800008-10810011), for runs performed in G104 (batches 108100001-108100004), Provide clarification regarding any differences in set-up that could account for the differences observed.

7.

8. Regarding provide the protocols for the The protocols should include the acceptance criterion for each parameter evaluated.

9. Regarding provide the protocols for the validation. The protocols should define conditions under which .

10. Table 139 in Section 3.2.S.2.5 lists hold times and storage times for different . Provide quality data to support the hold times and storage times listed in table 139. If these holds/storage times are part of the Idarucizumab manufacturing process, the validated hold times should be included in section 3.2.S.2.2.

11. We note that, as mentioned in the description of the studies performed on (b) (4) and as listed in table 135, (b) (4) The data for these experiments are not included in the submission. Provide data to support removal of up to (b) (4).

12. The process flow diagrams in the description of manufacturing process and process controls (3.2.S.2.2) for (b) (4) list a number of in-process controls (IPC) for each of the steps; however, the limits are only included for some of the IPC in section 3.2.S.2.4. Update section 3.2.S.2.4 with IPC process limits for all IPC listed in the process flow diagrams included in section 3.2.S.2.2. If limits are not included for any of the IPC, justification should be provided.

13. Insufficient information was provided in the BLA regarding the qualification and requalification of your primary and working reference standards.

14. 21 CFR 610.14 states that an identity test must be performed on products after all labeling operations have been completed. Provide information on the identity test and

protocol used to confirm that identity testing of idarucizumab drug product meets this CFR requirement.

15. You have proposed a 30 month shelf life for the Idarucizumab Drug Product. Your licensing submission contains real time stability data extending through a maximum of 24 months. Please provide a time table for submission of real time stability data sufficient to support a 30 month shelf life.

16. Provide tables that detail the sampling plans for idarucizumab drug substance and drug product manufacturing. The tables should include information on the process step, the parameters tested/sampled for, and the number of units sampled. For information on final drug product release and stability sampling, your response should include number of vials sampled, position within the filling order of a lot, and justification for your sampling plan.

If you have questions, call Melinda Bauerlien, Regulatory Business Process Manager at (301) 796-0906.

Sincerely,

Chana Fuchs -S

Digitally signed by Chana Fuchs -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Chana Fuchs -S, 0.9.2342.19200300.100.1.1=2000601863
Date: 2015.06.16 13:08:02 -04'00'

Chana Fuchs, Ph.D.
Team Lead
Division of Biotechnology Research and Review IV
Office of Biotechnology Products
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 761025

MID-CYCLE COMMUNICATION

Boehringer Ingelheim Pharmaceuticals, Inc.
Attention: Michelle Kliewer, RN, RAC
Director, Regulatory Affairs
900 Ridgebury Road
P.O. Box 368
Ridgefield, CT 06877

Dear Ms. Kliewer:

Please refer to your Biologic License Application (BLA) submitted under section 351(a) of the Public Health Service Act for Praxbind (idarucizumab) Injection, 2.5 gm/50mL (50 mg/mL).

We also refer to the teleconference between representatives of your firm and the FDA on May 27, 2015. The purpose of the teleconference was to provide you an update on the status of the review of your application.

A record of the teleconference is enclosed for your information.

If you have any questions, call Alycia Anderson, Regulatory Project Manager at (240) 402-4270.

Sincerely,

{See appended electronic signature page}

Kathy Robie Suh, MD, PhD
Clinical Team Lead
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Enclosure:
Mid-Cycle Communication

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MID-CYCLE COMMUNICATION

Meeting Date and Time: May 27, 2015 9:00 a.m. – 10:00 a.m. (ET)

Application Number: BLA 761025
Product Name: Praxbind (idarucizumab)
Indication: Reversal of the anticoagulant effects of dabigatran
Applicant Name: Boehringer Ingelheim Pharmaceuticals, Inc.

Meeting Chair: Kathy Robie Suh, MD, PhD
Meeting Recorder: Alycia Anderson, CCRP

FDA ATTENDEES

Office of Hematology and Oncology Products (OHOP)
Richard Pazdur, MD, Director

Office of Hematology and Oncology Products (OHOP)/Division of Hematology Products
Ann T. Farrell, MD, Director
Kathy Robie Suh, MD, PhD, Clinical Team Leader
Andrew Dmytrijuk, MD, Clinical Reviewer
Theresa Carioti, MPH, Chief, Regulatory Project Managers
Alycia Anderson, CCRP, Regulatory Project Manager
Jacquin Jones, CDR, BSN, MS, USPHS Regulatory Project Manager

OHOP/Division of Hematology Oncology Toxicology
Christopher Sheth, PhD, Pharmacology/Toxicology Supervisor
Emily Place, PhD, Pharmacology/Toxicology Reviewer

Office of Biotechnology Products/Division of Biotechnology Review & Research IV
Chana Fuchs, PhD, Acting Review Chief
Tura Camilli, PhD, Product Quality Reviewer
Lixin Xu, MD, PhD, Product Quality Reviewer
Frederick Mills, PhD, Product Quality Reviewer

Office of Clinical Pharmacology/Division of Clinical Pharmacology I
Rajnikanth Madabushi, PhD, Team Leader
Martina Sahre, PhD, Clinical Pharmacology Reviewer
Jeffry Florian, PhD, Team Leader (Division of Pharmacometrics)

Office of Surveillance and Epidemiology/Division of Risk Management
Carolyn Yancey, MD, Reviewer

Office of Surveillance and Epidemiology/Division of Medication Error Prevention Analysis
Teresa McMillan, PharmD, Reviewer

Eastern Research Group, Inc.
Christopher A. Sese

APPLICANT ATTENDEES

Dr. Dennis Blank, Quality Control, Germany
Dr. Marcus Branschaedel, Operations Biopharma, Germany
Dawn Collette, US Regulatory Affairs
Dr. Axel Dienemann, Global Regulatory Affairs
Holly Dursema, Nonclinical Drug Safety
Dr. Guanfa Gan, Metabolism and Pharmacokinetics
Dr. Stephan Glund, Medical Pharmacokinetics and Pharmacodynamics
Dr. Fredrik Gruenenfelder, Global Medicine Cardiovascular
Dr. Roland Guenther, Global Regulatory Affairs, CMC
Dr. Daniela Kasulke, Global Project Manager CMC
Dr. Michael Kraft, Head of Global Regulatory Affairs
Prof Dr. Joerg Kreuzer, Global Medical Lead Cardiovascular
Dr. Monika Kroez, Global Project Manager R & D
Rene Kubiak, Head of US Statistics
Dr. Bojan Lalovic, US Pharmacometrics
Dr. Sabine Luik, Senior Vice President US Medicine & Regulatory Affairs
Dr. Kiran Maass, Medical Writer
Dr. Lisa Matzen, Global Regulatory Affairs
Dr. Stephen Norris, Global Project Lead Bioanalysis
Dr. Stephen Olson, US Pharmacometrics
Dr. Joanne Palmisano, US Regulatory Affairs
Michael Pannucci, Project programmer
Dr. Claude Petit, Vice President US Biometrics and Data Management
Heidi Reidies, US Regulatory Affairs
Dr. Paul Reilly, Global Medical Lead Idarucizumab
Dr. Janet Schnee, US Medicine Cardiovascular
Dr. Nils Schoof, Global Epidemiology
Dr. Sabine Schiemann, CMC, Germany
Ingrid Schulz, Global Project Manager
Dr. Karen Sitney, US Regulatory Affairs, CMC
Dr. Joachim Stangier, Project Biomarker Expert
Dr. Georg van_Husen, Global Marketing Cardiovascular
Dr. Bushi Wang, Co-Project Statistician
Dr. Susan Wang, Project Statistician
Dr. Peter_Sebastian Zilles, Global Pharmacovigilance

Dr. Kristina Zint, Global Epidemiology

1.0 INTRODUCTION

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may or may not be able to consider your response before we take an action on your application during this review cycle.

2.0 SIGNIFICANT ISSUES

Clinical
The sponsor requests a full waiver of pediatric studies in patients age birth to 18 years because the studies would be impossible or highly impractical because the anticipated number of pediatric patients requiring reversal of the anticoagulant effects of dabigatran for emergency surgery/urgent procedures or in situations of life-threatening or uncontrolled bleeding is very small. The sponsor has not provided sufficient evidence to support that the pediatric studies for idarucizumab would be impossible or highly impractical. The sponsor should provide additional evidence and rationale that studies for idarucizumab would be impossible or highly impractical.

Discussion:
The Agency stated the Applicant will need to provide additional rationale and information regarding the pediatric study plan (PSP). The information submitted will be discussed internally with the Pediatric Review Committee (PeRC) and recommendation will then be sent to the sponsor. Boehringer Ingelheim Pharmaceuticals, Inc. acknowledged the Agency's request.

3.0 INFORMATION REQUESTS

Chemistry, Manufacturing, and Controls
A CMC IR was sent to sponsor on May 14, 2015; response is due June 4, 2015. Another IR will be sent to sponsor in June.

Discussion:
The Applicant stated that they will be responding to the pending Agency's request via email by June 4, 2015, and asked if the specific BLA sections can be updated with all CMC responses in a single amendment to the BLA file. The FDA agreed that providing responses in module 1.11 while updating the relevant module 3 sections at a later time based on the comprehensive responses would be acceptable.

4.0 MAJOR SAFETY CONCERNS/RISK MANAGEMENT

Clinical
A limited clinical safety database is currently available to support the BLA 761025 idarucizumab marketing application. Safety data from 26 patients from the Phase 3 protocol (1321.3) was submitted with the initial BLA application. No important safety concerns have been identified during the review at this point. The sponsor stated that additional safety data from 64 additional patients who have been enrolled in study 1321.3 will be submitted with the 120-day Safety Update Report.

Discussion:
Boehringer Ingelheim Pharmaceuticals, Inc. acknowledged the Agency's statement.

Division of Risk Management
The Division of Risk Management (DRISK) has no safety issues to communicate to the applicant. At this time, we do not anticipate the need for a risk evaluation and mitigation strategy (REMS) for idarucizumab.

Discussion:
Boehringer Ingelheim Pharmaceuticals, Inc. acknowledged the Agency's statement.

5.0 ADVISORY COMMITTEE MEETING

Clinical
No Advisory Committee Meeting is expected at this time.

Discussion:
Boehringer Ingelheim Pharmaceuticals, Inc. acknowledged the Agency's statement.

6.0 LATE-CYCLE MEETING /OTHER PROJECTED MILESTONES

Late Cycle Communication: July 27, 2015, 3:00 p.m. – 4:00 p.m. (ET)

Communicate Proposed Labeling: July 30, 2015

Inspection at Boehringer Ingelheim Pharmaceuticals, Biberach, has been scheduled for August 3 – 11, 2015.

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/s/

KATHY M ROBIE SUH
06/01/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 761025

INFORMATION REQUEST

Boehringer Ingelheim Pharmaceuticals, Inc.
Attention: Michelle Kliewer, RN, RAC
Director, Regulatory Affairs
900 Ridgebury Road
P.O. Box 368
Ridgefield, CT 06877

Dear Ms. Kliewer:

Please refer to your Biologics License Application (sBLA) dated February 20, 2015, received February 20, 2015, submitted under section 351(a) of the Public Health Service Act for Idarucizumab solution for injection/infusion (50 mg/mL).

We are reviewing your submission and have the following request for information. We request a written response by June 4, 2015 in order to continue our evaluation of your application.

1. **Description of the Manufacturing Process and Process Controls**
   For each step of the manufacturing process, (b) (4) specify:
   (b) (4)
2. **Control of Critical Steps and Intermediates**
   (b) (4)

(b) (4)

3. **Process Validation and/or Evaluation – PPQ batches**

(b) (4)

4. **Process Validation and/or Evaluation –** (b) (4)

(b) (4)

5. **Specifications**
   Indicate if bioburden results are calculated as the sum of TAMC + TYMC. If not, please specify how they are calculated.

6. **Analytical Procedures**
   Provide a description of the drug substance bioburden and endotoxin methods.

7. **Validation of Analytical Procedures**

(b) (4)

f. In Sections 3.2.S.4.3 and 3.2.P.5.3 Validation of Analytical Procedures, for all compendial methods other than endotoxin and bioburden assays used for idarucizumab drug substance and drug product release and/or stability testing, limited information or no information was provided to show that product specific matrix does not interfere with the method. Submit relevant data to demonstrate that the compendial methods are suitable for intended use for idarucizumab drug substance and/or drug product testing.

8. **Batch Analyses**
Justify endotoxin results of batches 10810007, 10810007, 10810009 and 10810010 of (b) (4) U/mg (AC ≤ (b) (4) EU/mg).

9. **Container Closure System**
(b) (4)

If you have questions, call Melinda Bauerlien, Regulatory Business Process Manager at (301) 796-0906.

Sincerely,

Chana Fuchs -S

Digitally signed by Chana Fuchs -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Chana Fuchs -S, 0.9.2342.19200300.100.1.1=2000601863
Date: 2015.05.14 14:11:11 -04'00'

Chana Fuchs, Ph.D.
Team Lead
Division of Biotechnology Research and Review IV
Office of Biotechnology Products
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

MEMORANDUM OF CORRESPONDENCE

DATE: 4/22/15

APPLICATION NUMBER: BLA 761025
DRUG PRODUCT: Idarucizumab solution for injection/infusion (50 mg/mL)
BETWEEN:

Name:

Boehringer Ingelheim Pharmaceuticals, Inc.
Prof., Dr., Uwe Buecheler, Head of Biopharmaceuticals
Karen Sitney Ph.D., CMC Regulatory Affairs
Daniela Kasulke, Ph.D., Biopharmaceuticals Project Management
Martin Flauger, Biopharmaceuticals, Quality Control, Audits
Michelle Kliewer, RN, RAC, Regulatory Affairs
Ingrid Schulz, International Project Management
Sabine Luik, M.D., Medicine & Regulatory Affairs

AND

Name: Food and Drug Administration
Chana Fuchs, Ph.D., Team Lead, OBP, DBRR IV
Lixin Xu, Ph.D., Quality Reviewer, OBP, DBRR IV
Melinda Bauerlien, M.S., Senior Regulatory Business Process Manager, OPRO
Patricia Hughes, Ph.D., Acting Branch Chief, OPF/DMA
Reyes Candauchacon, Ph.D., Microbiology Reviewer, OPF/DMA
Donald Obenhuber, Ph.D., Facility Reviewer, OPF/DIA
Wayne Seifert, Ph.D., Facility Reviewer, OPF/DIA

In response to the proposed manufacturing timelines submitted by the sponsor, the Agency requested the tcon to discuss the current pending BLA timelines for manufacturing. (b) (4)

The Agency clarified that DS manufacturing should be in operations during the inspection and preferably in (b) (4) and that based on the submitted timeline, the ideal situation is to have the (b) (4) The Agency indicated that the most probable dates for inspection would be during the first half of August; if Idarucizumab cannot be scheduled for manufacturing (b) (4) during that time frame, it may be possible to inspect (b) (4) during the manufacturing of a product with a similar manufacturing process. The Agency requested a list of products manufactured (b) (4) during the month of August if it would not be possible to have idarucizumab manufactured (b) (4) during the inspection timeline.

The Sponsor indicated that they would submit a list of products manufactured during that timeframe.

The sponsor responded that the drug product facility [redacted] (b) (4) The Agency verified that this would be acceptable as the DP facility has a positive compliance status and because idarucizumab DP manufacturing is not complex and is similar to other products made at the same facility. However, if needed, documentation of DP manufacturing will be looked at during the inspection.

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 761025

FILING COMMUNICATION –
NO FILING REVIEW ISSUES IDENTIFIED

Boehringer Ingelheim Pharmaceuticals, Inc.
Attention: Michelle Kliewer, RN, RAC
Director, Regulatory Affairs
900 Ridgebury Road
P.O. Box 368
Ridgefield, CT 06877

Dear Ms. Kliewer:

Please refer to your Biologics License Application (BLA) dated February 19, 2015, received February 19, 2015, submitted under section 351(a) of the Public Health Service Act for idarucizumab.

We also refer to your amendments dated December 22, 2014 and April 2, 7, and 10, 2015.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 601.2(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Priority**. Therefore, the user fee goal date is October 19, 2015. This application is also subject to the provisions of "the Program" under the Prescription Drug User Fee Act (PDUFA) V (refer to: http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm272170.htm).

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: *Good Review Management Principles and Practices for PDUFA Products*. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing requirement/commitment requests by July 30, 2015. In addition, the planned date for our internal mid-cycle review meeting is May 15, 2015. We are not currently planning to hold an advisory committee meeting to discuss this application.

At this time, we are notifying you that, we have not identified any potential review issues. Please note that our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

PRESCRIBING INFORMATION

Your proposed prescribing information (PI) must conform to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57. As you develop your proposed PI, we encourage you to review the labeling review resources on the *PLR Requirements for Prescribing Information* website including:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents
- The Selected Requirements for Prescribing Information (SRPI) − a checklist of 42 important format items from labeling regulations and guidances and
- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

At the end of labeling discussions, use the SRPI checklist to ensure that the PI conforms with format items in regulations and guidances.

PROMOTIONAL MATERIAL

We will review this application under the provisions of 21 CFR 601 Subpart E – *Accelerated Approval of Biological Products for Serious or Life-Threatening Illnesses*. Unless we otherwise inform you, as required by 21 CFR 601.45, you must submit during the preapproval review period copies of all promotional materials, including promotional labeling and advertisements, intended for dissemination or publication within 120 days following marketing approval (i.e., your launch campaign). During the preapproval review period, please submit, in triplicate, a detailed cover letter (list each proposed promotional piece in the cover letter along with the material type and material identification code, if applicable), the proposed promotional materials in draft or mock-up form with annotated references, and the proposed package insert (PI). Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Do not submit launch materials until you have received our proposed revisions to the package insert (PI) and you believe the labeling is close to the final version.

For more information regarding OPDP submissions, please see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm. If you have any questions, call OPDP at 301-796-1200.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We acknowledge receipt of your request for a full waiver of pediatric studies for this application. Once we have reviewed your request, we will notify you if the full waiver request is denied and a pediatric drug development plan is required.

If you have any questions, call Alycia Anderson, Regulatory Project Manager, at (240) 402-4270.

Sincerely,

{See appended electronic signature page}

Ann T. Farrell, MD
Director
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

THERESA A CARIOTI
04/20/2015
Signing on behalf of Dr. Ann Farrell

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 761025

INFORMATION REQUEST

Boehringer Ingelheim Pharmaceuticals, Inc.
Attention: Michelle Kliewer, RN, RAC
Director, Regulatory Affairs
900 Ridgebury Road
P.O. Box 368
Ridgefield, CT 06877

Dear Ms. Kliewer:

Please refer to your Biologics License Application (sBLA) dated February 20, 2015, received February 20, 2015, submitted under section 351(a) of the Public Health Service Act for Idarucizumab solution for injection/infusion (50 mg/mL).

We are reviewing your submission and have the following request for information. We request a written response by April 7, 2015 in order to continue our evaluation of your application.

The production schedule provided in the BLA cover letter dated February 20, 2015 provides a high level overview of the Idarucizumab manufacturing schedule. Please provide an updated production schedule which should include all primary operations for both upstream and downstream drug substance processes that are planned to occur during the months of June through September.

If you have questions, call Melinda Bauerlien, Regulatory Business Process Manager at (301) 796-0906.

Sincerely,

{See appended electronic signature page}

Chana Fuchs, Ph.D.
Team Lead
Division of Biotechnology Research and Review IV
Office of Biotechnology Products
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

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/s/

CHANA FUCHS
03/31/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 761025

BLA ACKNOWLEDGMENT

Boehringer Ingelheim Pharmaceuticals, Inc.
Attention: Michelle Kliewer, RN, RAC
Director, Regulatory Affairs
900 Ridgebury Road
P.O. Box 368
Ridgefield, CT 06877

Dear Ms. Kliewer:

We have received your Biologics License Application (BLA) submitted under section 351(a) of the Public Health Service Act (PHS Act) for the following:

Name of /Biological Product:	Idarucizumab Solution, 50 mg/mL
Date of Application:	February 19, 2015
Date of Receipt:	February 19, 2015
Our Reference Number:	BLA 761025

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on April 20, 2015 in accordance with 21 CFR 601.2(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 601.14(b) in structured product labeling (SPL) format as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action. The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

You are also responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No, 110-85, 121 Stat. 904).

The BLA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Hematology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

Secure email between CDER and applicants is useful for informal communications when confidential information may be included in the message (for example, trade secrets or patient information). If you have not already established secure email with the FDA and would like to set it up, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications.

If you have any questions, call me at (240) 402-4270.

Sincerely,

{See appended electronic signature page}

Alycia Anderson, BS, CCRP
Regulatory Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

ALYCIA C ANDERSON
03/04/2015

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

BLA 761025

PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE

Boehringer Ingelheim Pharmaceuticals, Inc.
900 Ridgebury Road
P.O. Box 368
Ridgefield, CT 06877

ATTENTION: Michelle Kliewer
Director, Regulatory Affairs

Dear Ms. Kliewer:

Please refer to your Biologics License Application (BLA) dated and received December 22, 2014, submitted under section 351(a) of the Public Health Service Act for Idarucizumab, 2.5 g/50 mL.

We also refer to your correspondence, dated and received December 22, 2014, requesting review of your proposed proprietary name, Praxbind.

We have completed our review of the proposed proprietary name, Praxbind and have concluded that it is acceptable.

If any of the proposed product characteristics as stated in your December 22, 2014, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Sarah Harris, Senior Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (240) 402-4774. For any other information regarding this application, contact Alycia Anderson, Regulatory Project Manager in the Office of New Drugs, at (240) 402-4270.

Sincerely,

{See appended electronic signature page}

Todd Bridges, RPh
Deputy Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

TODD D BRIDGES
01/18/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 112278

MEETING MINUTES

Boehringer Ingelheim Pharmaceuticals, Inc.
Attention: Michelle Kliewer, RN, RAC
Director, Regulatory Affairs
900 Ridgebury Road, P.O. Box 368
Ridgefield, CT 06877

Dear Ms. Kliewer:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Idarucizumab solution for injection/infusion (50 mg/mL).

We also refer to the meeting between representatives of your firm and the FDA on October 14, 2014. The purpose of the meeting was to discuss your drug development program including planned submission strategy and plans for expediting the development strategy.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Jessica Boehmer, Regulatory Project Manager at (301) 796-796-5357.

Sincerely,

{See appended electronic signature page}

Kathy Robie Suh, MD, PhD
Clinical Team Leader
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type:	B
Meeting Category:	Pre-BLA
Meeting Date and Time:	October 14, 2014; 9:00 AM – 10:00 AM ET
Meeting Location:	10903 New Hampshire Avenue White Oak Building 22, Conference Room: 1419 Silver Spring, Maryland 20903
Application Number:	IND 112278
Product Name:	Idarucizumab solution for injection/infusion (50 mg/mL).
Indication:	BI is developing idarucizumab as a reversal agent for the anticoagulant effect of dabigatran. The proposed indication is for use in patients treated with dabigatran etexilate who have uncontrolled bleeding or life-threatening bleeding requiring urgent intervention, and in patients who require emergency surgery/procedures when rapid reversal of the anticoagulant effects of dabigatran is required.
Sponsor/Applicant Name:	Boehringer Ingelheim Pharmaceuticals, Inc.
Meeting Chair:	Kathy Robie Suh, MD, PhD
Meeting Recorder:	Jessica Boehmer, MBA

FDA ATTENDEES

Office of Hematology and Oncology Products, Division of Hematology
Ann Farrell, MD, Director
Kathy Robie-Suh, MD, PhD, Clinical Team Leader
Nicole Verdun, MD, Clinical Reviewer
Jessica Boehmer, MBA, Senior Regulatory Project Manager

Office of Biotechnology Products, Division of Monoclonal Antibodies
Chana Fuchs, PhD, Product Quality Team Leader
Lixin Xu, MD, PhD, Product Quality Reviewer

Office of Clinical Pharmacology, Division of Clinical Pharmacology V
Atik Rahman, PhD, Director
Vicky Hsu, PharmD, Clinical Pharmacology Reviewer

Office of Biostatistics, Division of Biometrics V
Lola Luo, PhD, Statistical Reviewer

Office of Manufacturing and Product Quality
Patricia Hughes, PhD, Microbiology, Team Leader
Steven Fong, PhD, Microbiologist
Maria Reyes Candau-Chacon, PhD, Biologist

Division of Cardiovascular and Renal Products
Norman Stockbridge, MD, Director

EASTERN RESEARCH GROUP ATTENDEES

Patrick Zhou, Independent Assessor, Eastern Research Group

SPONSOR ATTENDEES

Boehringer Ingelheim
Dawn Collette, MBA, US Regulatory Affairs
Christopher Corsico, MD, MPH, Corp. Clinical Development, Medicine and Quality
Ulrich Drees, PhD, Corp. International Project Management
Klaus Dugi, MD, Corp. Medicine
Stephan Glund, PhD, Corp. Clinical PK/PD
Daniela Kasulke, PhD, Corp. CMC Project Management
Michelle Kliewer, RN, RAC, US Regulatory Affairs
Joerg Kreuzer, MD, Corp. Medicine
Monika Kroez, DVM, PhD, Corp. R&D Project Management
Sabine Luik, MD, US Medicine & Regulatory Affairs
Steven Olson, PhD, US Pharmacometrics
Michael Pannucci, US Project Programming
Claude Petit, PhD, US Statistics
Paul Reilly, PhD, US Medicine
Joanne vanRyn, PhD, Corp. Pharmacology
Ingrid Schulz, Corp. International Project Management
Karen Sitney, PhD, US Regulatory Affairs, CMC
Bushi Wang, PhD, US Statistics
Susan Wang, PhD, US Statistics
Axel Dienemann, PhD, Global Regulatory Affairs

1.0 BACKGROUND

Idarucizumab is a humanized antibody fragment (Fab) molecule derived from a IgG1 isotype molecule, directed against dabigatran.

Boehringer Ingelheim Pharmaceuticals, Inc. (BI) is developing idarucizumab as a reversal agent for the anticoagulant effect of dabigatran. The proposed indication is for use in patients treated with dabigatran etexilate who have uncontrolled bleeding or life-threatening bleeding requiring

urgent intervention, and in patients who require emergency surgery/procedures when rapid reversal of the anticoagulant effects of dabigatran is required.

Breakthrough Therapy Designation was granted for the indication above on June 16, 2014. The purpose of this meeting is a multidisciplinary comprehensive discussion of the drug development program, including the planned submission strategy and plans for expediting the development strategy.

The objectives of the meeting are:

- To discuss the adequacy of the proposed information package to support a Biologic License Application (BLA) submission and accelerated approval
- To gain agreement on the biomarker to be considered a surrogate for the assessment of clinical benefit to support accelerated approval
- To discuss post-marketing activities
- To discuss the Chemistry, Manufacturing, and Controls (CMC) development and gain agreement on manufacturing strategies and stability plan
- To discuss general considerations for manufacturing and product quality and nonclinical and clinical inspection considerations
- To discuss the rolling review and the plan to request Priority Review

Boehringer Ingelheim intends to request accelerated approval as described in 21CFR 601.41 for idarucizumab based upon the volunteer data and nonclinical data. BI plans to initiate the submission in December 2014 with the last key information to complete the BLA submitted in February 2015.

2. DISCUSSION

2.1. CMC

Question 1:

The chemistry, manufacturing, and controls information will be organized in the ICH Common Technical Document (CTD) format in Module 3 of the BLA. Documents that are planned to be submitted in the BLA are outlined in the DRAFT Table of Contents for Module 3 (Appendix 11.1).

Does the Division have any comments about the general organization and/or proposed content to be included in Module 3 of the BLA?

FDA Response to Question 1:

We have the following comments regarding the organization and content of module 3:

1. ***A master batch record is identified under section 3.2.P.3.3 rather than in section 3.2.R. It is not clear why a master batch record is included in this section. Please also see reply to question 2 regarding batch records.***

2. ***Sections 3.2.S.and 3.2.P should provide a tabular listing of all lots manufactured as well as the genealogy of each lot showing batch/lot number, date of manufacture, manufacturing site, manufacturing process, disposition QC status (for example, whether the batch was released, pending, quarantined, rejected). For drug product (DP) lots, identify the lot(s) of drug substance (DS) from which they originate.*** (b) (4) ***For each lot of DS and DP, identify the clinical protocols in which each lot was used as well as any other uses for these lots such as stability studies, toxicology studies, formulation studies, lots intended to be marketed, etc.***

3. ***Sections 3.2.S.2.1 and 3.2.P.3.1 (manufacturers) should include the specific activities executed at each manufacturing and testing site, including listing the individual tests run at each site.***

4. ***In sections 3.2.S.2.2, 3.2.S.2.4, 3.2.P.3.3 and 3.2.P.3.4, provide detailed descriptions of each step in the manufacturing process including information on the equipment used*** (b) (4) ***and the control strategy that will be utilized.***

5. ***Section 3.2.S.2.4, as presented in the meeting package, appears to contain analytical procedures used for in process testing and does not identify the presence of other control strategies. This section, as well as section 3.2.P.3.4, should contain comprehensive control strategy information, for example, the in-process controls, critical process parameters, etc.***

6. ***Section 3.2.S.2.3 should include protocols to monitor ongoing stability of the MCB and WCB.***

7. ***Section 3.2.S.5 should include a requalification protocol for reference standards as well as any protocol for qualification of future reference standards.***

8. ***For validation or qualification studies and reports in sections 3.2.S.4.3 and 3.2.P.5.3, include product-specific validation parameters that are part of the compendial assay qualification and any assay transfer qualification reports for assays validated at another site.***

9. ***Include the protocols for those assays identified in sections 3.2.S.4.2 and 3.2.P.5.2***

10. ***For methods using EP compendial procedures that are non-harmonized with USP, information identifying that the EP method is equivalent or better for the intended purpose than the USP method should be included.***

11. ***Appendix 11.1 contains a duplication of section 3.2.S.2.2, one for*** (b) (4) ***We assume, but it is not specified, that that there will be*** (b) (4) ***However, we are not clear on the splitting of the upstream from the downstream process. Unless there is a specific reason to split upstream from downstream, these should be included under one section of 3.2.S.2.2, and the information may be split within this section under different nodes as relevant for the different manufacturing steps. Please make sure that each node***

and section is titled to identify the specific content (e.g. 3.2.S.2.2 – process (b) (4) *of each section, node and document.*

12. *Include information in sections 3.2.P.3.3 and 3.2.P.5.1 on the process and specifications that fulfil the identity testing requirements per 21 CFR 610.14.*
13. *Additional guidance is provided under "Additional Comments"*

Discussion:

No discussion occurred.

Question 2:

BI proposes to submit one executed batch record (EBR) from one batch of drug substance per commercial manufacturing facility, and one executed batch record of the corresponding drug product primary stability batches manufactured at the commercial manufacturing site in Biberach, Germany. The selected EBRs will be representative of the commercial manufacturing process.

Does FDA agree with the number and the selection of the executed batch records for the BLA submission?

FDA Response to Question 2:

One executed batch record for DS and DP manufactured by the intended marketing process (including scale and facility) should be included in the BLA. Our understanding is that BI intends to submi (b) (4) ***The executed batch records should be representative of the commercial process. If this understanding is correct, the proposal is acceptable.***

If the original executed batch records are not in English, copies of executed batch records written in the original language should be submitted along with translated versions of the executed batch records.

Discussion:

FDA stated that Batch Records should be reflective of the to-be-licensed process.

Question 3:

As outlined in Question 22, BI is proposing a rolling review, with Module 3 and 4 information being submitted in December 2014 and submission of the formal complete BLA with the remaining Module 1, 2 and 5 information, in February 2015.

Stability data available at the time of Module 3 submission in December 2014, and at the time of the complete BLA submission in February 2015 are shown in Table 1 below. BI proposes that the additional stability data available in February 2015 be included with the complete BLA submission in February 2015. This additional data will include 12 months long-term, real time stability data for the primary stability lots, and 24 months long-term, real time stability data for (b) (4) L clinical lots fully representative of the commercial process. Although not designated as primary stability batches, these (b) (4) L clinical batches are equivalent to the primary stability batches and will be used to support designation of the shelf life of 30 months. Supportive stability data from (b) (4) L clinical batches will also be available in the Module 3 submission.

BI understands that according to PDUFA V, the submission of additional data, with FDA's agreement, should occur within 30 days of the date of the complete BLA submission. There will be no additional stability data on the primary stability batches or the (b) (4) L clinical batches available in this timeframe. 36 months stability data from the supportive (b) (4) L clinical lots shown in Table 1 could be provided in May, 2015.

Table 1 Stability data provided with BLA

Drug substance	**No. of DP lots**	**Long term stability data provided with Module 3 submission (December 2014)**	**Long term stability data provided with complete BLA submission (February 2015)**
Primary stability batches ((b) (4) L)	4	9 months	12 months
Clinical batches from (b) (4) L scale	2	18 months	24 months
Clinical batches from (b) (4) L scale	2	24 months	none

BI will provide the additional stability data as shown in Table 1 to support our proposed shelf life claim of 30 months at a storage temperature of 2-8 °C. Comparability between the primary stability batches and clinical batches has been demonstrated (see Section 10.1.1.7 and Appendix 11.2).

a) Does the Agency agree to this proposal?

FDA Response to Question 3a:

Submission of the proposed stability data with the complete BLA submission in February 2015 is acceptable.

Discussion:

No discussion occurred.

b) **Does the Agency agree that a shelf life of 30 months can be assigned for launch of idarucizumab solution for injection/infusion 50 mg/mL, on the basis of the primary stability batches and the (b) (4) L clinical batches?**

FDA Response to Question 3b:

No. FDA cannot agree to a 30 month expiration dating or make any conclusion on shelf life of the DP until the full manufacturing and stability data packages are reviewed.

The ability to assign a DP expiration dating of 30 months based primarily on 12 months stability data from 4 primary stability lots (process validation lots) manufactured at the commercial manufacturing site, Biberach (b) (4) (3 DP lots made from (b) (4) and 1 DP lot made from (b) (4)) and 24 months stability data from two clinical lots manufactured at the commercial manufacturing site from DS (b) (4) will depend on an assessment, during review of the BLA, of whether manufacturing of the clinical lots is fully representative of and simulating the commercial manufacturing processes that will be included in the BLA, and whether the stability data for DS and DP from (b) (4) are sufficiently similar to data from lots made by the (b) (4)

Sponsor should also ensure that data available from accelerated stability are from conditions that would enable a comparison of degradation rates for this product in its various manufacturing paradigms, especially if expiration dating for Drug Product is to be supported by material manufactured by the clinical manufacturing process.

Discussion:

No discussion occurred.

c) **Does FDA agree that the submission of the 36 month supportive stability data from the (b) (4) L clinical batches would be of benefit for the review of the proposed shelf life, and that BI should plan to submit these additional data in May 2015?**

FDA Response to Question 3c:

Although additional data from the clinical batches may be useful, specifically if there may be residual uncertainties from the data in the BLA, under PDUFA V, data should not be submitted more than 30 days after the submission of the original application unless it is requested by the Agency. During the review period, the Agency may request submission of a "simple stability update." "Simple stability updates" are defined as stability data and analyses performed under the same conditions and for the same drug product batches in

the same container closure system(s) as described in the stability protocol provided in the original submission. Furthermore, the "simple stability update" will use the same tabular presentation as in the original submission, as well as the same mathematical or statistical analysis methods (if any), and will not contain any matrix or bracketing approaches that deviate from the stability protocol in the original BLA. Whether the additional data from the (b) (4) L clinical batches are needed will be determined during the review period.

Discussion:

No discussion occurred.

Question 4:

The idarucizumab drug substance manufacturing process has been characterized and the process has been validated. All drug substance release criteria were met for a sum of nine process validation batches of drug substance (b) (4). Batches from a subsequent manufacturing campaign also met all drug substance release criteria, however did not show the expected (b) (4). BI has conducted an investigation of the root cause for the altered performance. As a final outcome of the investigations, BI intends to adjust some operational settings (b) (4). This will be confirmed under a formal validation protocol with pre-defined process validation limits covering only the adjustments (b) (4).

As stated above, validation has been completed for the entire manufacturing process, and this data will be provided with the Module 3 submission in December. In addition, BI proposes to submit the above mentioned protocol in the BLA in Section 3.2.S.2.5 with the Module 3 submission in December. As proposed above for the stability data, BI proposes that the additional validation data be included with the last submitted documents in February 2015.

Does the Agency agree to this proposal?

FDA Response to Question 4:

We cannot agree to the proposed plan at this time. The information submitted in the meeting package did not identify the root cause for (b) (4), and therefore, we cannot assess the relevance of the change to the rest of the manufacturing process and its validation, as well as to other CMC sections such as stability, specifications etc. Among the various causes that could result in the failures identified, (b) (4) are some of the possibilities.

The BLA should include information on the cause of the failure to meet the historical performance profiles and the initially validated process. Data should be provided on how the identified cause of failure and the subsequent modifications to the process may affect DS manufactured (b) (4) as well as assessment of any differences that may impact the downstream process, (b) (4)

[redacted] *For any differences noted, address whether these differences would or would not impact the validation of the downstream process.*
The BLA should include comprehensive characterization of DS lots manufactured by the modified upstream process in addition to the lot release data, and lots from this modified process should be placed on a stability protocol.

Data from the execution of the new validation protocol should also be available for review during the pre-license inspection.

Discussion:

The Agency expressed concern that the production problem was identified [redacted]. Sponsor stated that the processes [redacted] are the same except some small differences, [redacted] The Sponsor described their root cause analysis and measures they have taken to address the issue. The Agency commented that there is limited information at scale on the proposed remedy. The Sponsor will need to provide full details of the root cause analysis in the BLA. Whether there is a need for a fully validated process for [redacted] is a review issue. The information submitted will need to include characterization information for the product manufactured by the updated process. Information submitted should also include a description all differences, [redacted]. The Sponsor will provide a submission listing what CMC information will be submitted in the initial BLA (February) and what will be available in April.

2.2. Non-Clinical

Question 5:

The nonclinical information will be organized in the ICH Common Technical Document (CTD) format in Module 4 of the BLA. An overview of the planned pharmacology, pharmacokinetics, and toxicology documentation is provided in Appendix 11.1.

In addition, the BLA will contain summaries of available nonclinical information in Module 2 (2. 4, Nonclinical Overview; 2. 6, Nonclinical Summary).

Does the Division have any comments about the general organization and/or proposed content of nonclinical information to be included in the BLA?

FDA Response to Question 5:

We concur with the proposed organization and content of the nonclinical studies proposed for your BLA. In the BLA, reiterate your justifications for not conducting reproductive, developmental and carcinogenicity studies, and include relevant information about the

reproductive risks of using dabigatran. Also, please include both written and tabulated summaries in Section 2.6.

Discussion:

No discussion occurred.

2.3. Clinical

Question 6:

Boehringer Ingelheim (BI) is proposing to submit an idarucizumab BLA for accelerated approval as described in 21 CFR 601.41.

In two trials in volunteers, 1321.1 and 1321.2, an immediate and complete reversal of the anticoagulant effect of dabigatran, defined as the mean clotting times below the upper limit of normal (ULN) at the end of idarucizumab infusion, was observed with dTT, ECT, aPTT and TT. Similar data from the ongoing Phase 1 study 1321.5 is not yet available; however, interim data will be provided in the BLA.

The development program supports the use of idarucizumab in patients treated with dabigatran etexilate who have uncontrolled bleeding or who require emergency surgery/procedures when rapid reversal of the anticoagulant effects of dabigatran is required. Based on data from RE-LY, the coagulation markers ECT and aPTT are correlated with risk of bleeding.

Does the Agency agree that for the proposed use idarucizumab is expected to provide meaningful therapeutic benefit to patients over existing treatments, and thus may be considered for accelerated approval as described in 21 CFR 601.41?

FDA Response to Question 6:

Yes. Idarucizumab may be considered for accelerated approval.

Discussion:

No discussion occurred.

Question 7:

The currently proposed global clinical development program for idarucizumab is outlined in Section 10.3 of this document. The draft report synopsis for Study 1321.1 is provided as Appendix 11.3. The preliminary safety and PK/PD information from Study 1321.2 is provided in the draft report synopsis in Appendix 11.4. The available data show that idarucizumab immediately and completely reverses the anticoagulant effect of dabigatran,

suggesting that idarucizumab demonstrates a therapeutic effect that will provide a meaningful clinical benefit. BI is proposing to submit a BLA for accelerated approval based on:

- Complete data from Study 1321.1
- Complete data from Study 1321.2
- Interim data from ongoing Study 1321.5
- Data from ongoing Study 1321.3 as of cut-off date for the original BLA submission, provided as a structured patient profile and CRF for each patient.

Phase 1 studies 1321.1, 1321.2, and 1321.5 are designed to assess:

- safety, tolerability, pharmacokinetics, pharmacodynamics, and immunogenicity of idarucizumab
- effectiveness of idarucizumab in reversing dabigatran anticoagulant activity utilizing several anticoagulation tests, including aPTT, ECT and dTT
- re-administration of idarucizumab 2 months after an initial exposure (1321.2 only)
- re-administration of dabigatran etexilate 24h after the administration of idarucizumab (1321.2 only)

The single Phase 3 study (1321.3) is a multi-national single arm study investigating the safety and efficacy of idarucizumab in patients, initiated in May 2014. Since the prevalence of bleeds involving medical intervention and emergency procedures in patients taking dabigatran etexilate is unknown, it is anticipated that this study, despite the inclusion of several hundred centers, will take an extended period to be complete. BI proposes to provide a case report form and narrative for each patient treated with idarucizumab in 1321.3 as of the cut-off date for the BLA. The patient information will include:

- a description of each patient and their qualifying condition
- the outcome of the qualifying bleeding or emergency surgery and any other clinical outcomes or adverse events up to 2 weeks post-treatment
- where available the central biomarker results and dabigatran PK data
- the local biomarker results measuring the extent of reversal (local aPTT measurements are expected to provide real time qualitative information to the treating physician on reversal of dabigatran anticoagulant effects during the management of the patient)

Note that due to a 3-month follow-up period for safety and outcomes and at least a 2-month turnaround time for central laboratories, central biomarker results are not expected to be available for most of the entered patients at the time of data cutoff. In addition, the PK of idarucizumab as well as any anti-drug antibody (ADA) data for patients in this study are not planned to be available at the time of submission.

Only one other Phase I clinical study is expected to be ongoing at the time of the proposed BLA submission 1321.5. This is a study in healthy male Japanese volunteers. BI proposes to provide interim data from this study available at the data cut-off date for the BLA. This will include the PK/PD and safety data for approximately 80 volunteers. ADA and follow-up data will not be available for the interim report. The final 1321.5 clinical trial report will be submitted when available.

Based on the enrollment of subjects into studies 1321.1, 1321.2, and 1321.5, it is estimated that a safety database of over 280 subjects will be available at time of BLA submission, with exposure to idarucizumab in 230 of those subjects (including 16 elderly subjects and 18 subjects with renal dysfunction). Of these 230 subjects, approximately 62 subjects will have been exposed to the clinical dose of 5 g or greater. This together with the safety data from a limited number of treated patients from Study 1321.3 (e.g. 10-20 patients), will form the basis of our safety analysis for the registration dossier.

In addition to the clinical trial data outlined above, BI proposes to include the following clinical documentation in the idarucizumab BLA to support the assessment of its clinical efficacy and safety:

- Clinical Overview (2.5)
- Summary of Biopharmaceutics and Associated Analytical Methods (2.7.1)
- Summary of Clinical Pharmacology (2.7.2)
- Summary of Clinical Efficacy (2.7.3)
- Summary of Clinical Safety (2.7.4)

Because the primary evidence of efficacy will be based on biomarker data which will be presented in Module 2.7.2, only a limited Summary of Clinical Efficacy (2.7.3) will be included, for completeness. There is no formal ISS or ISE planned. Results of Phase I studies will be evaluated on a per trial basis, but also grouped together for further safety evaluations. Given the differences in the subjects and dosage, and dosing intervals the individual studies are considered to speak for themselves with respect to their ability to provide the required evidence. Documents that are planned to be submitted in the BLA are outlined in the DRAFT Table of Contents in Appendix 11.1.

Does the Agency concur with the clinical information package proposed to be included in a BLA for idarucizumab to support accelerated approval as described in 21 CFR 601.41?

FDA Response to Question 7:

In order to better understand the safety and efficacy of idarucizumab in as broad a group of subjects as possible, we recommend that an ISE and ISS for the available studies 1321.1, 1321.2 and 1321.5 should be included with your application. Differences in subject exposures should be explained in these documents.

FDA understands that complete data from study 1321.3 may not be available at the time of your BLA submission. However, for study 1321.3 where available for reported patients, time from dabigatran to idarucizumab dose should be included.

We note that, the number of elderly patients to be included in the submitted safety data base appears small. Adequacy of the safety database will be a review issue.

Discussion:

The Sponsor explained all information included in ISE and ISS will also be included in other sections of the BLA. FDA commented that it understands there may be some redundancy among the sections. However, an ISE and ISS should be included.

The Sponsor asked for clarification of the FDA comment regarding the number of elderly patients in the safety database being small. FDA stated it seemed there would be fewer than 20 elderly patients, but there is no required minimum number. Adequacy of the safety database is a review issue. The Sponsor stated there would be more (about 30) elderly patients in the submission.

Question 8:

Reversal of dabigatran effects will be based on changes in several anticoagulation tests supported by measurements of unbound dabigatran. Maximum reversal in the first 4 hours will be characterized and the durability of the effect will be based on measurements out to 72 hours.

In Study 1321.1, complete reversal (defined as the mean coagulation measurement of the dose group below the upper limit of normal) was achieved with idarucizumab doses of 1g, 2g, and 4g and complete or nearly complete reversal was sustained for up to 72 h in the 2g and 4g dose groups. In study 1321.2, results indicate that complete reversal was achieved with all doses (1 g, 5 g, 2.5+2.5 g) and complete reversal persisted for up to 72 h in the 5 g and the 2.5+2.5 g dose groups, including elderly subjects and subjects with renal insufficiency. Further details on these results are provided in Appendix 11.5.

Does the Agency consider this sufficient to form the basis for dosing recommendations and demonstration of reversibility of dabigatran anticoagulant effect in the registration dossier?

FDA Response to Question 8:

Whether or not the data submitted will be sufficient to support the safety and efficacy of idarucizumab for the reversibility of dabigatran anticoagulant effect will be a review issue. However, the preliminary data submitted to date appear to support the proposed recommended dosing of idarucizumab.

Discussion:

No discussion occurred.

Question 9:

Boehringer Ingelheim is using two primary biomarkers in the idarucizumab development program to assess the extent of dabigatran reversal after administration of idarucizumab:

Ecarin Clotting Time (ECT) and diluted Thrombin Time (dTT). These biomarkers, coupled with direct measurement of concentrations of total ("sum") and free ("unbound sum") dabigatran will be the basis for demonstrating reversal of the anticoagulant effect of dabigatran. In addition, aPTT and thrombin clotting time will also be measured to assess reversal of the anticoagulant effect of dabigatran.

ECT and aPTT are identified in the US prescribing information for PRADAXA (dabigatran etexilate mesylate) capsules as a possible measurement to assess the degree of anticoagulant activity of dabigatran, based on results of RE-LY.

Diluted thrombin time is measured with the Hemoclot® Direct Thrombin Inhibitors Assay (Hyphen BioMed, France). It has received a CE mark in the European Union and other countries, but is not registered in the US. The main purpose of dTT measurements in this clinical program is to demonstrate reversal of dabigatran-mediated anticoagulation based on its readout of coagulation time.

The original IND submission for idarucizumab included a summary of the assay qualification results and performance characteristics for both ECT and dTT for the measurement of the pharmacodynamic effects of dabigatran. Prolongation of ECT and dTT display a linear relationship with dabigatran plasma concentrations and directly reflect the dabigatran concentrations in plasma.

To support accelerated approval of idarucizumab in the US, BI currently proposes to rely on ECT as a surrogate for the assessment of clinical benefit of idarucizumab as a reversal agent for the anticoagulant effect of dabigatran. Acknowledging that other countries may consider dTT as the more appropriate surrogate endpoint, BI is planning to present both ECT and dTT results in the global registration documentation for idarucizumab. Both will be supported by direct measurement of free ("unbound sum") dabigatran in plasma.

a) Does the Agency in principle concur that ECT may be considered a surrogate for the assessment of clinical benefit to support accelerated approval of idarucizumab as a reversal agent for the anticoagulant effect of dabigatran in bleeding patients and patients requiring emergency procedures?

FDA Response to Question 9a:

Possibly. This will be a review issue.

Discussion:

No discussion occurred.

b) Please comment on the acceptability of dTT as a potential surrogate for accelerated approval.

FDA Response to Question 9b:

Hemoclot which measures dTT is not registered in the US as you note above. Therefore, the use of dTT to support a safety or efficacy claim for idarucizumab would be considered supportive rather than primary.

Discussion:

No discussion occurred.

Question 10:

The planned analyses for the integrated summary of data for the evaluation of reversal are described in Section 10.4. The table of contents and actual display templates of these planned analyses are provided in Appendix 11.6 and 11.7. The proposed primary and secondary efficacy analyses are based on the results obtained from the volunteer studies 1321.1, 1321.2 and 1321.5.

a) Does the Agency have further comments regarding the provided analysis plan?

b) Does the Agency concur that the proposed primary and secondary efficacy analyses are adequate?

FDA Response to Questions 10a and 10b:

The proposed primary and secondary analyses appear to be appropriate. Additional analyses may be requested during review if needed. You should clearly indicate in the initial BLA database submission for each subject the number of idarucizumab doses received.

In addition, you should perform safety analyses where all adverse events are considered for the primary safety analysis regardless of attribution.

Discussion:

No discussion occurred.

Question 11:

The trials to be included in the complete SCS and the groupings of studies to be presented in Module 2.7.4, Summary of Clinical Safety (SCS) as well as in the supporting tables located in Module 5.3.5.3 are outlined in Section 10.4, and the table of contents of the actual analyses are provided in Appendix 11.8.

Does the Division have any comments regarding the proposed groupings of studies proposed for the SCS and the provided Statistical Analysis Plan?

FDA Response to Question 11:

The proposed groupings appear to be acceptable.

Discussion:

No discussion occurred.

Question 12:

For the 4-month Safety Update Report, BI plans to use a cut-off date which is near the date of the BLA submission (target December 2014); based on current planning, the safety update will include more than 4 months additional data from studies 1321.3 and 1321.5.

For Study 1321.3, we propose to update the information on the use of idarucizumab in patients by providing available structured patient profiles and a tabular overview of all treated patients. The structured patient profiles will be primarily focused on the first 2 weeks of patient treatment and management, when local biomarkers are available to assess reversal and when we anticipate most of the events will occur.

For Study 1321.5, we propose to provide the final clinical trial report and replacement of updated datasets.

BI does not intend to submit updated exposure tables for the dossier, nor plans to update any tables presented in the SCS provided with the original BLA. We will provide updated tables and tabulations to support the evaluation of safety.

It is planned to update the US proposed draft labeling with the final 1321.5 follow-up safety and the ADA data. Supporting tables will be provided in Module 5.3.5.3.

Does the FDA agree with the proposed data cut-off and the scope of data to be included in the 4-month Safety Update Report?

FDA Response to Question 12:

We agree with the proposed cut-off date for the Safety Update Report. However, in order to better understand the safety and efficacy of idarucizumab in as broad a group of subjects as possible we recommend that a complete analysis of study 1321.5 be submitted with the initial BLA submission along with the data from the completed studies 1321.1 and 1321.2. See response to Question 7 as well.

Discussion:

No discussion occurred.

Question 13:

It is expected that the patient study 1321.3 will be ongoing during the review period. If idarucizumab is granted accelerated approval based on the effect on a surrogate endpoint, it is intended to continue the accrual of reversal and clinical data in patients in the 1321.3 study during and after the registration process to document any clinical benefit. Study 1321.3 potentially provides confirmation of the clinical benefit by:

- summarizing bleeding outcomes and mortality
- in the potential subset of patients where bleeding can be visualized, temporal correlation of reversal markers with actual stoppage of bleeding
- exploring investigator assessments about the clinical impact of administering the antidote
- assess hemodynamic measurements in unstable patients when dabigatran effects are reversed
- estimate blood volumes in patients with hemorrhagic stroke or ICH where serial scans are available

The detailed analysis plan for study 1321.3 is included in Appendix 11.9.

a) Does the Agency agree that the completion of 1321.3 could provide confirmation of the clinical benefit?

FDA Response to Question 13a:

Adequacy of the study is result dependent.

Discussion:

No discussion occurred.

b) Does the Agency have any comments or proposals for these activities?

FDA Response to Question 13b:

Not at this time. Also, see FDA Response to Question 13a, above.

Discussion:

No discussion occurred.

Question 14:

Modules 2.7.1, Summary of Biopharmaceutic Studies and Associated Analytical Methods and 2.7.2, Summary of Clinical Pharmacology Studies in the idarucizumab BLA will summarize clinical pharmacology information for idarucizumab, including relevant assay

methodologies and biomarkers. Appendix 11.10 and Appendix 11.11 provide these summary outlines for review.

Does the Division concur with the proposed approach for clinical pharmacology information to be provided in the BLA?

FDA Response to Question 14:

Yes.

Discussion:

No discussion occurred.

Question 15:

A compartmental pharmacokinetic binding model characterizing the time course of dabigatran and idarucizumab will be provided in Module 2.7.2. This model is based on a model of the digoxin-Fab (DigiFab) interaction as described by Balthasar, et. al., and will be developed using all PK data from 1321.1, 1321.2 and 1321.5. Because these studies are all Phase 1 healthy subject studies, covariate assessment will be confined to basic risk factors: creatinine clearance, age, weight, sex (19 female subjects in 1321.2), race (primarily Caucasian and, due to inclusion of 1321.5, Japanese) as well as prior exposure to idarucizumab.

The sum dabigatran exposure-response relationship for dTT, ECT, aPTT and TT will be evaluated in a separate analysis rather than as a PK/PD component of the model described above. However, in addition to observed sum dabigatran these analyses will include PK model predicted sum dabigatran which is not available bioanalytically in the presence of idarucizumab. As with the pharmacokinetic model, covariate assessment will be confined to basic risk factors: creatinine clearance, age, weight and race as well as prior exposure to idarucizumab.

Appendix 11.12 provides the proposed pharmacometric analysis plan for review.

a) **Does the Division have comments regarding the proposed analysis plan?**

FDA Response to Question 15a:

Your proposed plan is reasonable.

Discussion:

No discussion occurred.

b) Does the Division agree with the approach proposed for evaluating the dabigatran-idarucizumab pharmacokinetic interactions and dabigatran exposure-response relationships?

FDA Response to Question 15b:

Yes. The proposed approach is reasonable.

Discussion:

No discussion occurred.

Question 16:

BI proposes to provide in the BLA case report forms (CRFs) and structured patient profiles for all available patients from Study 1321.3. An example of a structured patient profile is provided in Appendix 11.13.

For studies 1321.1, 1321.2, and 1321.5, BI will include CRFs and narratives for:

- Volunteers who died or experienced a serious adverse event
- Volunteers who experienced adverse events of special interest
- Volunteers who permanently discontinued study medication due to an adverse event.

Narratives for other events of interest identified during the review will be provided upon request.

Does the Division agree with this proposal?

FDA Response to Question 16:

Yes. The proposal appears to be acceptable.

Discussion:

No discussion occurred.

Question 17:

In general, all summary documents will be provided as text-based PDF files. Each summary document will contain bookmarks that match the document table of contents, and hypertext links to each item listed within the TOC. Our application will include a thorough table of contents and working hyperlinks that are clearly written and relevant to the review referencing capability both within a document and through hyperlinks, between documents in an application, submission, or submission unit.

For the 1321.1, 1321.2, and 1321.5 reports, patient narratives (as described in Question 16) will be provided within the body of the report. However, structured patient profiles and CRFs related to 1321.3 from all patients will be supplied in a Module 5.3.4.2. When CRFs are provided for a study, these CRFs will be located in the associated study folders.

Study data in electronic format will be provided for 1321.1, 1321.2, and 1321.5. The case report tabulations and analysis datasets for the studies will be located within the datasets folder in Module 5 in the respective study folders. It is planned to provide integrated analysis datasets for the Summary of Clinical Pharmacology, Pharmacokinetic (PK), Summary of Clinical Safety and Summary of Clinical Efficacy.

BI currently uses SAS version 9.2. The tabulations and analysis subfolders will each include SAS transport files (XPT) version 5 and a data definition table file (define.xml) as documentation of the datasets and all corresponding SAS programs. An annotated case report form (blankcrf.pdf) will also be provided within the tabulations folder for each of the studies.

In the datasets for all trials, adverse events and diagnoses in the electronic datasets will be coded in MEDDRA version 17.0, and therapies will be coded according to the WHO-DD version MAR:14.

The proposed e-submission package will include the below items from trials 1321.1, 1321.2 and interim 1321.5:

- Data tabulations per clinical study (CDISC SDTM version 1.3, Implementation Guide (IG) version 3.1.3)
- Project level ADaM datasets used to produce the SCE and SCS appendix tables
- Lab data using the US units at the project level for selected lab parameters see Appendix 11.14
- Lab data in SI units at trial level
- MeDRA version 17.0 will be used for AEs and baseline information
- As the 1321.1, 1321.2 and 1321.5 trials are all single-center clinical pharmacology studies, the Summary Level Clinical Site Dataset will not be provided

Does the Division concur with this proposal?

FDA Response to Question 17:

Yes. The proposal appears to be acceptable.

In addition to submitting SAS programs for the analysis datasets (i.e. ADaM files), the SAS programs that are used for the efficacy data analysis should also be included in the BLA submission.

Discussion:

No discussion occurred.

Question 18:

On April 9, 2014, BI submitted a response to the FDA with the information of the mechanism underlying the reported saturation of reuptake/catabolism processes in the kidneys with higher BI 655075 doses, which was requested in the meeting minutes from the February 11, 2014 pre-IND meeting. The BI April 9, 2014 response can be found in Appendix 11.15.

Does the Division have any questions or comments concerning this response?

FDA Response to Question 18:

No.

Discussion:

No discussion occurred.

2.4. Regulatory

Question 19:

The sponsor acknowledges FDA guidance which provides that consumers and/or health care providers should not be routinely required to use more than one vial to administer a typical single dose of the drug product. Commercial product is planned to be provided as two 50R vials in one carton supporting a single dose for a single patient. There is no other primary package in development.

Does the Agency agree that commercial product will be provided as two 50R vials in one carton supporting a single dose for a single patient?

FDA Response to Question 19:

Although you can package two vials per carton, the labeling of the vial and carton as a single dose for a single patient will be a review issue based on the Dosage and Administration Section of the Package Insert Labeling.

Discussion:

No discussion occurred.

Question 20:

On-site inspection is one of many tools the FDA has for ensuring the integrity of data, the health and welfare of research participants, and the protection of public health.

Can the Agency provide insight into planned inspections related to this dossier?

FDA Response to Question 20:

DHP is currently reviewing your submission, and may request clinical study site inspections, in the course of DHP's review.

Discussion:

No discussion occurred.

Question 21:

The Sponsor is looking for opportunities ahead of the BLA submission to familiarize the FDA with development program, and proposes to keep communication open with the Division regarding:

- Project status on major activities
- Project schedule
- Status of issues and risks
- Status of action items, if applicable
- Future or planned activities

The intent is to inform FDA reviewers of the project's progress providing sufficient detail to allow reviewers to make informed decisions/recommendations and maintain knowledge/oversight of the project.

a) **Does the Agency have any suggestions that the sponsor might consider to enhance transparency and facilitate activities?**

FDA Response to Question 21a:

We encourage communication with us as you describe. We have no other recommendations at this time.

Discussion:

No discussion occurred.

b) **Does the Division intend to have an Application Orientation Presentation meeting to present the pivotal information that supports the idarucizumab BLA?**

FDA Response to Question 21b:

Yes. You should plan to present an Application Orientation Meeting.

c) Would the Agency consider the option of a rolling submission for the idarucizumab BLA? If so, please comment on the acceptable "granularity" of the pre-submissions (e.g., see Question 22)

Discussion:

No discussion occurred.

FDA Response to Question 21c:

Rolling submission is acceptable. However, you will need to submit complete reviewable modules. Please also see the response to question 22,

Discussion:

No discussion occurred.

Question 22:

Per the Guidance for Industry- *Expedited Programs for Serious Conditions- Drugs and Biologics*, BI would request the Agency to consider accepting portions (complete modules) of the BLA prior to the full BLA submission targeted for February 2015. BI would propose the following schedule for submission:
December 19, 2014 Module 3 and QOS; Module 4 and Nonclinical overview
December – February Module 5 Clinical Trial Reports and datasets as they are finalized
February 20, 2015 Module 1, remaining Module 2

We anticipate that the last key information to complete the BLA will be ready for submission in February 2015.

Does the Agency agree to this rolling review? Is the proposed schedule for submission acceptable?

FDA Response to Question 22:

Rolling submission is acceptable, in principle. However, you will need to submit complete reviewable modules. The proposed schedule and modules do not include sufficient detail for agreement on a rolling BLA submission. You should identify and list the contents of each complete module and provide the time of submission for each module. For example, the "Dec-February" submission for module 5 clinical trial reports and datasets are not appropriately detailed, and may not constitute submission of a full reviewable unit. If there are specific sections that would benefit from different submission dates, the whole

reviewable unit should be specifically defined, contents listed and a date of submission identified.

Regarding submission of the CMC unit, please see our response to question 4. If additional data are available at this time to address the concerns specified regarding submission of the CMC unit in December, you may submit this information and FDA can provide a post-meeting response based on this additional information.

Discussion:

FDA emphasized that for agreement on a rolling submission, it needs to have a clear understanding of what will be coming in and when. Sponsor should submit a list containing the reviewable units and the planned dates of submission for each unit. The review clock will not initiate until the final module of the initial BLA submission has been received.

Question 23:

The company would be interested if the Agency has comments based upon experience with *Breakthrough Therapy Designation* and how labeling negotiations are approached.

The registration package is comprised of Phase I biomarker data and ADA as presented in the 2.7.2 Summary of Clinical Pharmacology and 2.7.4 Summary of Clinical Safety. It is planned to present Clinical Pharmacology in Section 12 Clinical Pharmacology of the proposed USPI. Adverse Reactions for the Phase I data will be presented in Section 6 of the USPI. No clinical study data is planned for inclusion in Section 14 of the USPI.

a) Does the Agency agree to this approach?

FDA Response to Question 23a:

Final text of the labeling is a review issue. Labeling discussions will be held at an appropriate time as the reviews near completion.

Discussion:

No discussion occurred.

BI has considered best case timelines and accelerated all process steps where possible to support an early launch of idarucizumab.

For common understanding, the following timelines apply under this accelerated approach:

- If the total labelling components are provided at one time (PDUFA), it will take 6-7 weeks for finishing of product to be supplied in the market.

- If the text of the vial label was approved earlier (separate from the US PI and folding box), this would potential shorten the finishing of the product to 5-6 weeks (vial label available 1-2 weeks prior to PDUFA).

In our process, the approval of the vial label must be obtained before we initiate activities as there is no option to revise it. Additionally, in our process the US PI and folding box are combined into one step. The folding box is closed either with tamper evidence label or glued which does not support the US PI to be added later.

If the total labeling components are approved 6-7 weeks prior to PDUFA, it is possible to have finished product in the market 3-4 days after FDA approval.

b) Would the Agency consider (b) (4) **?**

FDA Response to Question 23b:

No.

Discussion:

No discussion occurred.

Question 24:

Idarucizumab is a New Biologic Entity (NBE) for use in patients treated with dabigatran who have uncontrolled bleeding or life-threatening bleeding requiring urgent intervention, and in patients who require emergency surgery/procedures when rapid reversal of the anticoagulant effects of dabigatran is required. Because this is a therapeutic option with no approved drugs, BI assumes that the BLA will be subject to an Advisory Committee review.

Does the FDA have any comment on our assumptions regarding a potential Advisory Committee for idarucizumab?

FDA Response to Question 24:

An Advisory Committee meeting may be needed. This will be a review issue. However, if such a meeting is required FDA will inform you in a timely fashion.

Discussion:

No discussion occurred.

Question 25:

BI does not *a priori* plan to include REMS in the BLA submission. If FDA comes to the conclusion that a REMS is necessary we assume that this discussion can be resolved during the review of the BLA. BI is planning to request a priority review for the BLA.

Does the FDA have any comment or guidance to offer BI to assure that all discussions relating to a REMS be covered during the review period?

FDA Response to Question 25:

At this time, the Office of New Drugs and the Office of Surveillance and Epidemiology have insufficient information to determine whether a risk evaluation and mitigation strategy (REMS) will be necessary to ensure that the benefits of the drug outweigh the risks, and if it is necessary, what the required elements will be. We will determine the need fora REMS during the review of your application.

FDA recommends including in your submission the rationale for why a REMS is not required for this application.

Discussion:

No discussion occurred.

FDA ADDITIONAL COMMENTS:

We have the following additional comments to assist with the preparation of your BLA.

Product Quality Microbiology

The CMC Drug Substance section of the BLA (Section 3.2.S) should contain the following product quality microbiology information:

- Evidence of monitoring of bioburden and endotoxin levels at critical manufacturing steps using qualified bioburden and endotoxin tests. Bioburden samples should be collected prior to (b) (4) step and after hold. Pre-determined bioburden and endotoxin limits should be provided (3.2.S.2.4).
- Three successful product (b) (4) hold time validation runs at manufacturing scale. Bioburden and endotoxin levels before and after the maximum allowed hold time should be monitored and bioburden and endotoxin limits provided (3.2.S.2.5). Bioburden samples should be collected prior to (b) (4) step.
- (b) (4) sanitization and storage validation data and information (3.2.S.2.5).
- Bioburden and endotoxin data obtained during manufacture of the three conformance or PPQ batches (3.2.S.2.5).
- Summary of shipping validation studies and data (3.2.S.2.5).

- Drug substance bioburden and endotoxin release specifications. The bioburden limit should be [redacted] mL for bulk materials allowed to be stored for extended periods of time [redacted] (3.2.S.4).
- Qualification data for bioburden and endotoxin test methods performed for [redacted] and drug substance (3.4.S.4).
- The effect of hold time on endotoxin recovery should be assessed by spiking a known amount of endotoxin into undiluted drug substance and then testing for recoverable endotoxin over time. The studies should be conducted using containers of similar composition as those used for drug substance during hold. Effects of sampling containers on endotoxin recovery should also be evaluated.

Discussion:

Summary of shipping validation studies should be included in the BLA. The shipping studies should simulate real-time Drug Product shipping conditions. A surrogate for the product may be used.

The CMC Drug Product section of the BLA (Section 3.2.P) should contain validation data summaries supporting the aseptic process and sterility assurance. For guidance on the type of data and information that should be submitted, refer to the 1994 "FDA Guidance for Industry, *Submission Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products*".
The following study protocols and validation data summaries should be included in Section 3.2.P.3.5:

- Bacterial filter retention study for the sterilizing filter.
- Sterilization and depyrogenation of equipment and components that contact the sterile drug product. The equipment requalification program should be described.
- In-process microbial controls and hold times. Hold times should be validated at manufacturing scale.
- Isolator decontamination, if applicable.
- Three successful consecutive media fill runs, including summary environmental monitoring data obtained during the runs. Media fill and environmental monitoring procedures should be described.
- A description of the routine environmental monitoring program.
- Summary of shipping validation studies and data.

The following method validation information should be provided:

- Container closure integrity testing (3.2.P.2.5). System integrity (including maintenance of the microbial barrier) should be demonstrated for the complete manufacturing process. Container closure integrity methods validation should demonstrate that the assay is sensitive enough to detect breaches that could allow microbial ingress and should include routine manufacturing process defects as controls. We recommend that container closure integrity testing be performed *in lieu* of sterility testing for stability samples every 12 months (annually) and at expiry (3.2.P.8.2).

- Qualification data for bioburden, sterility and endotoxin test methods performed for in-process intermediates (b) (4) (where applicable) and the drug product, as appropriate (3.2.P.5).
- Rabbit Pyrogen Test data for three batches of drug product in accordance with 21 CFR 610.13(b).
- Formulations with certain excipient and polysorbate combinations have been reported to interfere with endotoxin recoverability in the USP LAL test methods over time. The effect of hold time on endotoxin recovery should be assessed by spiking a known amount of endotoxin into undiluted drug product and then testing for recoverable endotoxin over time. The studies should be conducted using containers of similar composition as those used for drug product during hold. Effects of sampling containers on endotoxin recovery should also be evaluated.

Discussion:

Results from a one time (b) (4) study using three batches of drug product should be included in the BLA. This is to ensure that no other (b) (4) are associated with the drug product. The determination of endotoxin masking effects in the drug product formulation should be conducted by spiking standard endotoxin (CSE or RSE) into undiluted product.

Inspection Readiness:

All facilities should be registered with FDA at the time of the BLA submission and ready for inspection in accordance with 21 CFR 600.21 and 601.20(b)(2). Please include in the BLA submission a complete list of manufacturing and testing sites with their corresponding FEI numbers. An updated manufacturing schedule for the bulk drug substance and drug product fill finish sites should be included in Module 1 of the BLA under section 1.3.

Discussion:

No discussion occurred.

3.0 OTHER IMPORTANT MEETING INFORMATION

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

- The content of a complete application was discussed.

  The Sponsor indicated they may submit CMC reports in April. They will provide a detailed submission outlining all CMC documents that will be included in the BLA submission, and those that will be submitted in April. The Review Team will review this submission upon receipt.

  All applications are expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities included or referenced in the application.

- A preliminary discussion on the need for a REMS was held and it was concluded that this will be a review issue.

  Also See FDA Response to Question 25.

- Major components of the application are expected to be submitted with the original application and are not subject to agreement for late submission. You stated you intend to submit a complete application and therefore, there are no agreements for late submission of application components.

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (PSP) within 60 days of an End of Phase (EOP2) meeting. In the absence of an End-of-Phase 2 meeting, refer to the draft guidance below. The PSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The PSP should be submitted in PDF and Word format.

For additional guidance on the timing, content, and submission of the PSP, including a PSP Template, please refer to the draft guidance for industry, *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans* at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf. In addition, you may contact the Pediatric and Maternal Health Staff at 301-796-2200 or email pdit@fda.hhs.gov. For further guidance on pediatric product development, please refer to: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm.

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57. As you develop your proposed PI, we encourage you to review the labeling review resources on the *PLR Requirements for Prescribing Information* website including:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of 42 important format items from labeling regulations and guidances.

Prior to submission of your proposed PI, use the SRPI checklist to ensure conformance with the format items in regulations and guidances.

MANUFACTURING FACILITIES

To facilitate our inspectional process, we request that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, "Product name, NDA/BLA 012345, Establishment Information for Form 356h."

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
1.				
2.				

Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
1.				
2.				

4.0 ISSUES REQUIRING FURTHER DISCUSSION

None

5.0 ACTION ITEMS

None

6.0 ATTACHMENTS AND HANDOUTS

The Sponsor's handout is attached.

13 Page(s) have been Withheld in Full as B4 (CCI/TS) immediately following this page

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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

KATHY M ROBIE SUH
11/05/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 112278

GRANT –
BREAKTHROUGH THERAPY DESIGNATION

Boehringer Ingelheim Pharmaceuticals Inc
Attention: Michelle Kliewer
Director, Regulatory Affairs
900 Ridgebury Road, P.O. Box 368
Ridgefield, CT 06877

Dear Ms. Kliewer:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Idarucizumab (BI 655075).

We also refer to your April 17, 2014, request for Breakthrough Therapy designation. We have reviewed your request and have determined that Idarucizumab (BI 655075) for use in patients treated with dabigatran who have uncontrolled bleeding or who require emergency surgery/procedures when rapid reversal of the anticoagulant effects of dabigatran is required meets the criteria for Breakthrough Therapy designation. Therefore, we are granting your request for Breakthrough Therapy designation. Please note that if the clinical development program does not continue to meet the criteria for Breakthrough Therapy designation, we may rescind the designation.

FDA will work closely with you to provide guidance on subsequent development of Idarucizumab (BI 655075) for for use in patients treated with dabigatran who have uncontrolled bleeding or who require emergency surgery/procedures when rapid reversal of the anticoagulant effects of dabigatran is required to help you design and conduct a development program as efficiently as possible. For further information regarding Breakthrough Therapy designation and FDA actions to expedite development of a designated product, please refer to section 902 of the Food and Drug Administration Safety and Innovation Act (FDASIA) and the draft *Guidance for Industry: Expedited Programs for Serious Conditions – Drugs and Biologics.*[1]

In terms of next steps, please submit a Type B meeting request. This meeting will be for a multidisciplinary comprehensive discussion of your drug development program, including planned clinical trials and plans for expediting the manufacturing development strategy. Attachment 1 lists potential topics for discussion at this initial breakthrough therapy meeting. Please refer to the *Guidance for Industry: Formal Meetings between FDA or Sponsors and*

[1] http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf

Applicants[2] for procedures on requesting a meeting. If you feel that submitting a meeting request for such a meeting at this point is pre-mature or if you have recently held a major milestone meeting, please contact the Regulatory Health Project manager noted below to discuss the timing of this meeting.

If the breakthrough therapy designation for Idarucizumab (BI 655075) for use in patients treated with dabigatran who have uncontrolled bleeding or who require emergency surgery/procedures when rapid reversal of the anticoagulant effects of dabigatran is required is rescinded, submission of portions of the BLA will not be permitted under this program. However, if you have Fast Track designation you will be able to submit portions of your application under the Fast Track program.

If you have any questions, contact Jessica Boehmer, Regulatory Project Manager, at (301) 796-5357.

Sincerely,

{See appended electronic signature page}

Ann T. Farrell, MD
Division Director
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Attachment:

Attachment 1: Possible Discussion Topics for the Initial Comprehensive Multidisciplinary Breakthrough Therapy Type B Meeting

[2] http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM153222.pdf

ATTACHMENT 1: Possible Discussion Topics for the Initial Comprehensive Multidisciplinary Breakthrough Therapy Type B Meeting

The following are possible discussion topics for the initial comprehensive multidisciplinary breakthrough therapy Type B meeting depending on the therapeutic area, development phase, and specific development program issues.

General and/or Regulatory

- The planned target date for NDA/BLA submission, including plans for rolling review
- The specific indication that studies are intended to support
- Other indications in development
- Expanded access plans, including the intent to communicate these plans publicly
- Plans to seek accelerated approval
- Regulatory status with non-U.S. regulatory agencies
- Plans to defer or waive specific studies (e.g., pediatric studies), including those to be conducted as postmarketing requirements/postmarketing commitments
- Critical aspects of proposed studies, including enrichment designs, non-inferiority designs, and historical controls, and any planned novel approaches
- Plans for submission of a proprietary name request
- If a drug/device combination product, the device development information and plan
- If the use of the drug will require a diagnostic test, the in vitro diagnostic development plan with the Center for Devices and Radiological Health (CDRH)
- The Gantt chart of the development timeline
- The proposed communication plan for managing interactions between CDER and the sponsor, including the timing and format of these interactions

Clinical and Statistical

- Existing and planned clinical sites and accrual data
- Efficacy:

- The status of all clinical trials and topline summary results
- The preliminary evidence of effectiveness
- The planned or completed clinical trials intended to support efficacy, including:

  - The overall trial design, the population to be studied, trial size, proposed indications, endpoints, power, plans for interim analyses, plans for resizing of trials or any other adaptation, type I error control, and expected initiation and completion dates.

  - The justification for all dose selections, including number of doses and dose intervals and a discussion of all clinical trials that will provide dose-response information.

  - The validity of the outcomes and endpoints. If using patient-reported outcomes or surrogate endpoints, support for those endpoints or plans to support or validate them, as necessary.

- Safety:

  - Potential safety issues from nonclinical studies and early clinical trials

  - Liver, kidney, cardiac, immune suppression, carcinogenicity, genotoxicity, reproductive and developmental, and immunogenicity safety profiles

  - The clinical trial safety monitoring plan for safety signals identified in nonclinical studies and early clinical trials, and for postmarketing drug safety and surveillance (pharmacovigilance)

    - The proposed size of the safety population
    - The plan or the need for long-term safety studies or trials

      - Preapproval
      - Postapproval

  - The plans to mitigate or minimize risk, proposed risk evaluation and mitigation strategies, if needed

- Specific populations:

  - The dose, trial design, efficacy endpoints, size and composition of the population, and additional safety trials for populations such as:

    - Elderly patients
    - Pediatric patients
    - Hepatically and renally impaired patients

- The proposed pediatric development plan with outlines and synopses of additional studies

Clinical Pharmacology and Pharmacokinetics

- The clinical pharmacology, pharmacodynamic, and pharmacokinetic trials: completed, ongoing, planned, and requests for deferral
  - Immunogenicity assessments
  - Dosing information from pharmacodynamics studies
    - Single ascending dose
    - Multiple ascending dose
    - Dose response study
  - Food-effect
  - Drug-drug interactions (DDI)
  - Thorough QT/QTc
  - Pharmacokinetic studies in patients with renal or hepatic dysfunction
  - Pharmacogenomics
- The plans for an in vivo bridging trial of the formulation studied in the clinical development program to the to-be-marketed formulation
- The plans for conducting population pharmacokinetics, exposure-response modeling and simulation analyses
- The plans to describe dose modifications in labeling based on DDI, age, organ impairment, among others

Nonclinical Pharmacology, Pharmacokinetics, and Toxicology

- The nonclinical studies completed, ongoing, and planned, including the number and sex of animals per dose, doses, route of administration, toxicities, duration of study, and study results. For planned studies, the timelines for initiation and submission of study reports. Examples of such studies include:
  - Subacute and chronic toxicology and associated toxicokinetics
  - Genetic toxicology
  - Reproductive and developmental toxicology
  - Carcinogenicity studies

- Animal models of disease and pharmacokinetic parameters associated with efficacy
- Evidence of mechanism of action
- Absorption, distribution, metabolism, and excretion
- Safety pharmacology, where appropriate

Chemistry, Manufacturing, and Controls

- Drug product:
  - The dosage form
  - The formulation description
  - Administration instructions, delivery systems (e.g., vials, prefilled syringes) proposed draft packaging, and disposal instructions
  - Critical quality attributes
  - The control and stability strategies
  - The proposed shelf life and required stability studies
- Drug substance:
  - Characterization
  - Critical quality attributes
  - The control and stability strategies
  - The proposed shelf life or retest period and required stability studies
- Proposed commercial processes:
  - The manufacturing process, in-process controls, scale-up plans
  - A comparison of the proposed commercial manufacturing process to the clinical manufacturing process
  - Comparability of lots used in clinical trials and commercial lots or a plan to establish analytical comparability
  - The current manufacturing site(s) and proposed commercial site(s), if different, registration numbers, readiness, and manufacturing timelines
  - The current release and stability testing site(s) and proposed commercial testing site(s), if different

- The anticipated market demand at launch

- Proposed validation approaches:

  - The drug substance and drug product manufacturing process
  - Microbial control and sterility assurance
  - Viral clearance
  - The analytical methods

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/s/

ANN T FARRELL
06/16/2014

LATE-CYCLE COMMUNICATION DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 761025

LATE-CYCLE MEETING MINUTES

Boehringer Ingelheim Pharmaceuticals, Inc.
Attention: Michelle Kliewer, RN, RAC
Director, Regulatory Affairs
900 Ridgebury Road
P.O. Box 368
Ridgefield, CT 06877

Dear Ms. Kliewer:

Please refer to your Biologic License Application (BLA) submitted under section 351 of the Public Health Service Act for Praxbind (idarucizumab) Solution, 50 mg/mL.

We also refer to the Late-Cycle Meeting (LCM) between representatives of your firm and the FDA on July 27, 2015.

A copy of the official minutes of the LCM is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Alycia Anderson, Regulatory Project Manager at (240) 402-4270.

Sincerely,

{See appended electronic signature page}

Kathy Robie Suh, MD, PhD
Clinical Team Leader
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Enclosure:
Late Cycle Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF LATE-CYCLE MEETING MINUTES

Meeting Date and Time: July 27, 2015, 2:00 p.m. – 3:00 p.m. (ET)
Meeting Location: 10903 New Hampshire Avenue
White Oak Building 22, Conference Room: 1309
Silver Spring, Maryland 20903

Application Number: BLA 761025
Product Name: Praxbind (idarucizumab)
Applicant Name: Boehringer Ingelheim Pharmaceuticals, Inc.

Meeting Chair: Kathy Robie Suh, MD, PhD
Meeting Recorder: Alycia Anderson, CCRP

FDA ATTENDEES

Office of Hematology and Oncology Products
Richard Pazdur, MD, Director

Office of Hematology and Oncology Products/Division of Hematology Products
Ann T. Farrell, MD, Director
Kathy Robie Suh, MD, PhD, Clinical Team Leader
Andrew Dmytrijuk, MD, Clinical Reviewer
Theresa Carioti, MPH, Chief, Project Management Staff
Alycia Anderson, CCRP, Regulatory Project Manager
CDR Jacquin Jones, USPHS, BSN, MS, Regulatory Project Manager

OHOP/Division of Hematology, Oncology, Toxicology
Christopher Sheth, PhD, Pharmacology/Toxicology Supervisor
Emily Place, PhD, Pharmacology/Toxicology Reviewer

Office of Biotechnology Products/Division of Biotechnology Review & Research I and IV
Chana Fuchs, PhD, Acting Review Chief
Tura Camilli, PhD, Product Quality Reviewer
Lixin Xu, MD, PhD, Product Quality Reviewer
Frederick Mills, PhD, Product Quality Reviewer

Office of Clinical Pharmacology/Division of Clinical Pharmacology I
Martina Sahre, PhD, Clinical Pharmacology Reviewer
Jeffry Florian, PhD, Team Leader (Division of Pharmacometrics)
Dinko Rekic, PhD, MSc (Pharm), Pharmacometrics Reviewer

Office of Surveillance and Epidemiology/Division of Risk Management
Carolyn Yancey, MD, Reviewer

EASTERN RESEARCH GROUP ATTENDEES
Christopher A. Sese

APPLICANT ATTENDEES
Dawn Collette, US Regulatory Affairs
Dr. Axel Dienemann, Global Regulatory Affairs
Dr. Stephan Glund, Medical Pharmacokinetics and Pharmacodynamics
Dr. Daniela Kasulke, Global Project Manager CMC
Prof Dr. Joerg Kreuzer, Global Medical Lead Cardiovascular
Dr. Joanne Palmisano, US Regulatory Affairs
Heidi Reidies, US Regulatory Affairs
Dr. Paul Reilly, Global Medical Lead Idarucizumab
Ingrid Schulz, Global Project Manager
Dr. Karen Sitney, US Regulatory Affairs, CMC
Dr. Susan Wang, Project Statistician

1.0 BACKGROUND

BLA 761025 was submitted on February 19, 2015 for Praxbind (idarucizumab).

Proposed indication: Reversal of the anticoagulant effects of dabigatran.

PDUFA goal date: October 19, 2015

FDA issued a Background Package in preparation for this meeting on July 15, 2015.

2.0 DISCUSSION

1. Introductory Comments

   Welcome was extended and Introductions were made. The objectives of the meeting were stated as described in the Late-Cycle Meeting Background Package.

   Discussion:
   No further discussion during meeting.

2. Discussion of Substantive Review Issues

   Chemistry, Manufacturing and Controls (CMC) - Outstanding issues were identified in an information request (IR) sent on July 10, 2015, and are still pending response and review at the time the late cycle meeting document was finalized. Items 1b, 1c, 2, 10, 12, 14, 15 of that request need to be appropriately resolved prior to any approval action.

Discussion:
Outstanding issues were identified in an IR sent on July 10, 2015, and are pending response and review at the time this document was finalized.

With the exception of item 1c that remains unresolved and will require additional discussion, all other items from the July 10, 2015 IR appear to have been addressed appropriately.

3. Discussion of Minor Review Issues

CMC review has not been completed at the time that this late cycle meeting package was finalized, and therefore, some points may have not yet been identified. Outstanding issues were itemized in an IR sent on July 10, 2015. Those IRs that were not listed under Substantive Review Issues above, need to be resolved but some could be addressed through postmarketing commitment(s) (PMCs) or other post approval mechanisms if necessary.

Discussion:
The review is still ongoing. An additional IR will be sent to address additional minor issues.

4. Information Requests

   a. NEW DMEPA IR –As proposed in your labeling, the recommended dose of idarucizumab is 5 grams, provided in two vials, each containing 2.5 gm/50 mL. From a medication error standpoint, we are concerned that healthcare practitioners may not administer the entire dose as packaged due to the fact that one dose is comprised of two separate vials. Therefore, under doses may occur. Provide a rationale for the current packaging of two 2.5 gram vials instead of a one 5 gram vial. Additionally, provide information regarding patient outcomes if only 2.5 grams instead of 5 grams is administered.

   Discussion:

   The Agency commented on possible confusion with marketing a presentation containing less than one full dose.

   Post Meeting Discussion:

   The Applicant stated that they would work on submitting the response to this IR.

   b. CMC - An IR document was sent on July 10, 2015, and is pending response and review at the time the late cycle meeting document was finalized.

   Discussion:
   No further discussion during meeting.

5. Discussion of Upcoming Advisory Committee Meeting

   An Advisory Committee meeting is not planned.

   Discussion:
   No further discussion during meeting.

6. REMS or Other Risk Management Actions

   No issues related to risk management measures that would need a risk evaluation and mitigation strategy (REMS) have been identified to date.

   Discussion:
   No further discussion during meeting.

7. Postmarketing Requirements/Postmarketing Commitments

   Identification of all CMC associated PMCs has not yet been finalized at this time.

   Discussion:
   No further discussion during meeting.

   Post-meeting note:
   Review is ongoing and postmarketing requirements/postmarketing commitments are still under development.

8. Major Labeling Issues

   a. Clinical Pharmacology - Based on preliminary results from REVERSE-AD submitted as part of your BLA, orientation slides from your meeting with the FDA, and your recent publication in NEJM (Pollack et al., NEJM 2015), it appears that increases in dabigatran concentration and clotting times may have been observed within 24 hours in >10% of patients enrolled in your open-label observational study. How do you intend to instruct practitioners whose patients still show clinically relevant anticoagulation after receiving the labeled dose? Have you considered the inclusion of an option of additional dosing in such patients whose clotting parameters remain elevated, along with clinical signs related to bleeding, following the administration of proposed dose of idarucizumab?

      Discussion:
      The Applicant noted that while redistribution of dabigatran occurs in a subset of patients and that subsequent increases in clotting measurements can be observed in these patients, these increases in clotting measures are not necessarily clinically relevant. They had not considered how best to convey these

observations to practitioners. When asked what situations may warrant readministration of idaricizumab, the Applicant responded that two patients were readministered idaricizumab in ongoing study 1321.3. The Applicant suggested that patients who displayed both clinical signs of bleeding as well clotting test measurements reflective of anticoagulation may warrant readministration of idaricizumab. The review team acknowledged the Applicant's response and would consider the information during labeling.

b. Clinical - In order to better inform prescribers about the available safety database for idarucizumab, you should describe study 1321.3 in section 14 Clinical Studies and provide safety information for study 1321.3 in section 6 Adverse Reactions in the product label.

Discussion:
There was discussion that some information on experience with re-dosing may need to be included. Instances may occur where a patient experiences persistent increased clotting tests and bleeding or a surgical patient may need re-operation.

9. Review Plans

Complete reviews. Review and provide detailed comment on the proposed labeling.

Discussion:
FDA will complete the reviews and provide the Applicant with comments for the draft labeling and the Applicant will respond.

10. Wrap-up and Action Items

This application has not yet been fully reviewed by the signatory authority, division director, and Cross-Discipline Team Leader (CDTL) and therefore, this meeting did not address the final regulatory decision for the application.

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/s/

KATHY M ROBIE SUH
08/05/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 761025

LATE CYCLE MEETING
BACKGROUND PACKAGE

Boehringer Ingelheim Pharmaceuticals, Inc.
Attention: Michelle Kliewer, RN, RAC
Director, Regulatory Affairs
900 Ridgebury Road
P.O. Box 368
Ridgefield, CT 06877

Dear Ms. Kliewer:

Please refer to your Biologic License Application (BLA) submitted under the Public Health Service Act for Praxbind (idarucizumab) Solution, 50 mg/mL.

We also refer to the Late-Cycle Meeting (LCM) scheduled for July 27, 2015. Attached is our background package, including our agenda, for this meeting.

If you have any questions, call Alycia Anderson, Regulatory Project Manager, at (240) 402-4270.

Sincerely,

{See appended electronic signature page}

Kathy Robie Suh, MD
Clinical Team Leader
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

ENCLOSURE:
Late-Cycle Meeting Background Package

LATE-CYCLE MEETING BACKGROUND PACKAGE

Meeting Date and Time:	July 27, 2015, 2:00 p.m. – 3:00 p.m. (ET)
Meeting Location:	10903 New Hampshire Avenue White Oak Building 22, Conference Room: 1309 Silver Spring, Maryland 20903
Application Number:	BLA 761025
Product Name:	Praxbind (idarucizumab)
Indication:	Reversal of the anticoagulant effects of dabigatran.
Sponsor/Applicant Name:	Boehringer Ingelheim Pharmaceuticals, Inc.

INTRODUCTION

The purpose of a Late-Cycle Meeting (LCM) is to share information and to discuss any substantive review issues that we have identified to date, Advisory Committee (AC) meeting plans (if scheduled), and our objectives for the remainder of the review. The application has not yet been fully reviewed by the signatory authority, division director, and Cross-Discipline Team Leader (CDTL) and therefore, the meeting will not address the final regulatory decision for the application. We are sharing this material to promote a collaborative and successful discussion at the meeting.

During the meeting, we may discuss additional information that may be needed to address the identified issues and whether it would be expected to trigger an extension of the PDUFA goal date if the review team should decide, upon receipt of the information, to review it during the current review cycle. If you submit any new information in response to the issues identified in this background package prior to this LCM or the AC meeting, if an AC is planned, we may not be prepared to discuss that new information at this meeting.

BRIEF MEMORANDUM OF SUBSTANTIVE REVIEW ISSUES IDENTIFIED TO DATE

1. Discipline Review Letters

No Discipline Review letters have been issued to date.

2. Substantive Review Issues

CMC- Outstanding issues were identified in an IR sent on July 10, 2015, and are still pending response and review at the time this late cycle meeting document was finalized. See item 2 in the section below for specific points that could become substantive review issues.

ADVISORY COMMITTEE MEETING

An Advisory Committee meeting is not planned.

REMS OR OTHER RISK MANAGEMENT ACTIONS

No issues related to risk management measures that would need a risk evaluation and mitigation strategy (REMS) have been identified to date.

LCM AGENDA

1. Introductory Comments – 5 minutes (RPM/CDTL)

   Welcome, Introductions, Ground rules, Objectives of the meeting

2. Discussion of Substantive Review Issues – 5 minutes

   Each issue will be introduced by FDA and followed by a discussion.

   a. CMC: Outstanding issues were identified in an IR sent on July 10, 2015, and are pending response and review at the time this document was finalized. Items 1b, 1c, 2, 10, 12, 14, 15 need to be appropriately resolved prior to any approval action.

3. Discussion of Minor Review Issues – 10 minutes

   a. CMC review has not been completed at the time that this late cycle meeting package was finalized, and therefore, some points may have not yet been identified. Outstanding issues were itemized in an IR sent on July 10, 2015. Those IRs that were not listed in section 2, above, need to be resolved but some could be addressed through PMCs or other post approval mechanisms if necessary.

4. Information Requests – 5 minutes

   a. NEW DMEPA IR –As proposed in your labeling, the recommended dose of Idarucizumab is 5 grams, provided in two vials, each containing 2.5 g/50 mL. From a medication error standpoint, we are concerned that healthcare practitioners may not administer the entire dose as packaged due to the fact that one dose is comprised of two separate vials. Therefore, under doses may occur. Provide a rationale for the current packaging of two 2.5 gram vials instead of a one 5 gram vial. Additionally, provide information regarding patient outcomes if only 2.5 g instead of 5 g is administered.

   b. CMC- An IR document was sent on July 10, 2015, and is pending response and review at the time this late cycle meeting document was finalized.

5. Postmarketing Requirements/Postmarketing Commitments – 10 minutes
    a. CMC –identification of all CMC associated PMCs has not yet been finalized at this time.

6. Major labeling issues – 10 minutes

Clinical Pharmacology

Based on preliminary results from REVERSE-AD submitted as part of your BLA, orientation slides from your meeting with the FDA, and your recent publication in NEJM (Pollack et al., NEJM 2015), it appears that increases in dabigatran concentration and clotting times may have been observed within 24 hours in >10% of patients enrolled in your open-label observational study. How does the applicant intend to instruct practitioners whose patients still show clinically relevant anticoagulation after receiving the labeled dose? Has the applicant considered the inclusion of an option of additional dosing in such patients whose clotting parameters remain elevated, along with clinical signs related to bleeding, following the administration of proposed dose of Idarucizumab?

Clinical

In order to better inform prescribers about the available safety database for idarucizumab the applicant should describe study 1321.3 in section 14 Clinical Studies and provide safety information for study 1321.3 in section 6 Adverse Reactions in the product label.

7. Review Plans – 5 minutes

Complete reviews. Review and provide detailed comment on the proposed labeling.

8. Wrap-up and Action Items – 10 minutes

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/s/

KATHY M ROBIE SUH
07/15/2015